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Asymmetric Carbon−Carbon Coupling of Phenols or Anilines with Aryllead Triacetates

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Abstract: The asymmetric coupling of various phenol or aniline derivatives with bulky aryllead triacetates was thoroughly investigated using optically active amines, including strychnine and brucine. We found that conformationally restricted tertiary amines, as well as lithium aryloxides and molecular sieves, are essential for accelerating the rate of phenol coupling. Consequently, the reaction can be carried out at a low temperature (−40 to −20 °C) and gives a high degree of diastereo- and enantioselectivity. In contrast to the effectiveness of lithiation in phenol coupling, magnesation of anilines was a critical technique for aniline coupling with aryllead triacetates. Using these coupling methods, a diverse set of di-, tri, and polyaryl compounds with axial chirality can be easily obtained, and these should be useful for the construction of a variety of aryl−aryl frameworks involved in metal ligands, natural products, and artificial helical polymers.

Introduction

The optically pure biaryl axis has been the subject of increasing interest due to its role as a pivotal element in a rapidly growing number of not only pharmacologically potent natural products[1] (e.g., vancomycin, steganone, etc.) but also chiral catalysts[2] (e.g., BINAL-H, BINAP, etc.) and artificial helical polymers.[3] Despite a broad spectrum of classical[4] and modern[5] procedures for connecting aromatic moieties, the development of efficient aryl-coupling methods that enable the directed construction of even highly sterically demanding bi and polyaryls in optically active form[6] has become very important.

The major methods for the synthesis of these compounds can be divided into four categories: (1) Ullmann coupling of aryl halides,[7] (2) oxidative coupling of electron-rich phenols,[8] (3) nucleophilic aromatic substitution on electron-deficient arenes with arylmetal compounds,[9] and (4) transition-metal-catalyzed cross-coupling between aryl halides and arylmetal species.[10]

Optically active biaryls are often prepared by the intramolecular Ullmann coupling of two aryl halides linked by a chiral tether, and this enables the coupling between two different aromatics to give the asymmetrical biaryls.[8] In contrast, the intermolecular oxidative coupling of aromatic alcohols using metal salts ligated by optically active amines gives symmetrical biaryls, such as BINOL, with high enantioselectivity.[8c−f] Moreover, the successful extension of this class of reactions to the catalytic process, which involves cross-coupling between two different arenes[8h] in the presence of molecular oxygen,[8i,j] has recently been reported.

With the use of arylmetal reagents, nucleophilic aromatic substitution of aromatic compounds[9] that have both activating group and leaving groups was extensively studied by Meyers and co-workers.[9a−d] Using chiral oxazolines or chiral esters,[9f,g] accompanied by specific leaving groups such as menthol,[9e] asymmetrical biaryls in an optically active form can be synthesized diastereoselectively. Unfortunately, however, a very high atropisomeric excess is obtained with a pair of aromatic compounds in which the substituents *ortho* to the coupling position significantly differ in size.

The cross-coupling reactions between aryl halides or triflates and aryl boronic acids (Suzuki−Miyaura coupling)[5b] or Grignard

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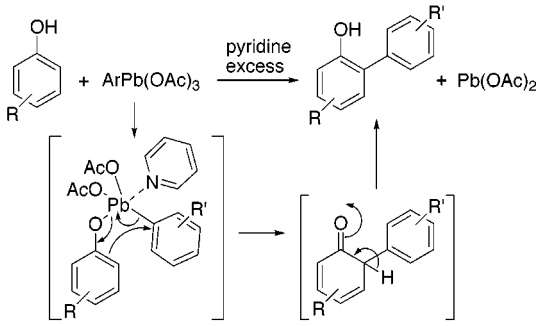
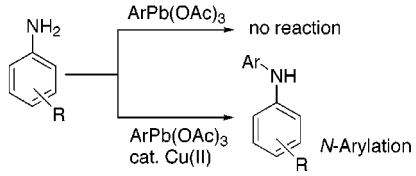
Scheme 1



Scheme 2



reagents (Kumada−Tamao coupling)[4a] with metal catalysts has been shown to be very useful for obtaining various biaryls.[10] Among the most outstanding examples to date are the use of Hayashi's chiral Ni catalysts[10a,b] and the method recently reported by Buchwald.[10c] However, the use of sterically congested substrates has frequently resulted in a significant decrease in yield, and thus these methods have shown limited scope. This is an inherent disadvantage, since axially chiral compounds are required to have steric bulk proximal to the chiral axis, around which conformational rotation is highly restricted. Uemura reported that Suzuki coupling using planar chiral arene chromium complexes gave relatively bulky biaryls in good yields with high diastereoselectivity.[10e,f]

Entirely different approaches have also been used to create optically active biaryl frameworks. The kinetic resolution of racemates with enzymes,[11] desymmetrization,[12] and the asymmetric ring-opening of achiral lactones[6a,c] have been shown to have wide-ranging applications. Despite the obvious usefulness of these methods, there is still a need for enantioselective cross-coupling using an external source of chirality, such as asymmetric catalysts.

Barton reported that the ligand coupling of phenols with arylleads is a powerful tool for synthesizing sterically hindered products under mild conditions.[13] The reaction using arylleads as an equivalent of aryl cation was originally devised by Pinhey, who demonstrated that the use of excess pyridine accelerated the reaction rate (Scheme 1).[14]

In marked contrast, anilines and anilides do not undergo either *C*- or *N*-arylation with aryllead triacetates.[15] Barton[16] and others[17] later reported that $Cu(OAc)_2$-catalyzed *N*-arylation of anilines using aryllead triacetates, which gave various *N*,*N*-diarylamines but did not lead to *C*-arylation (Scheme 2). On the basis of these findings, we report here that the asymmetric aryl−aryl coupling reaction with aryllead triacetate proceeded

Scheme 3

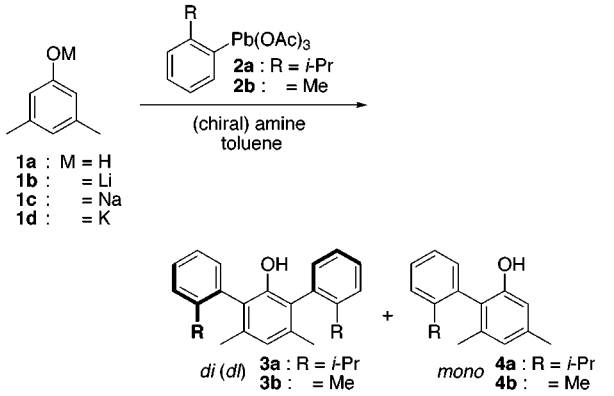
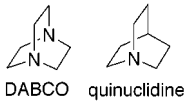


Table 1. Effect of Amine in the Ligand Coupling of **1a** with **2a**[a]



entry	amine	yield (%)[b]	*dl*-**3a**:*meso*-**3a**[c]
1	*i*-$PrNH_2$	75(7)	>99:<1
2	$(i\text{-Pr})_2NH$	0(31)	−
3	$(i\text{-Pr})_2Et$	0(10)	−
4	Et_3N	0(11)	−
5	DABCO	78	>99:<1
6	quinuclidine	95	>99:<1

[a] The reaction was performed using **1a** (1.0 equiv), aryllead compound **2a** (3.0 equiv) and amine (3.0 equiv) at rt for 2 h. Refer to Scheme 3. For experimental details, see Supporting Information. [b] Yields are of isolated, purified **3a**, and those in parentheses are of mono-coupling product **4a**. [c] The ratio of diastereomers of **3a**.

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Table 2. Effect of Chiral Amine in the Asymmetric Coupling of **1a** with **2a** or **2a**[a]

entry	aryllead	amine	yield (%)[b]	ee (%)[c]	entry	aryllead	amine	yield (%)[b]	ee (%)[c]
1	**2b**	**5**	99	0	10	**2b**	**9**	68	4
2	**2b**	**6**	48	0	11	**2b**	strychnine	99	15
3	**2b**	**7**	22	9	12	**2b**	brucine	99	14
4	**2b**	**8**	55	3	13	**2a**	**9**	14[d]	4
5	**2b**	sparteine	49	5	14	**2a**	**10**	16[d]	0
6	**2b**	dehydroabietylamine	99	6	15	**2a**	**11**	2[d]	6
7	**2b**	ajmalicine	16	0	16	**2a**	**12**	3[d]	0
8	**2b**	eburnamonine	36	0	17	**2a**	strychnine	32	20
9	**2b**	$(DHQD)_2PHAL$	55	3	18	**2a**	brucine	92	40

[a] The reaction was performed using **1a** (1.0 equiv), aryllead compound **2a** or **2b** (2.5 equiv), and amine (3.0 equiv) in toluene at rt. Refer to Scheme 3. For experimental details, see Supporting Information. [b] Unless otherwise specified, yields are of isolated, purified di-coupling product **3a** or **3b**. [c] Determined by HPLC analysis. [d] Of isolated, purified mono-coupling product **4a**.

Table 3. Effect of Solvent in the Asymmetric Coupling of **1a** with **2b**[a]

entry	solvent	time (h)	yield (%)[b]	*dl*-**3b**:*meso*-**3b**	ee (%)[c]
1	CH_2Cl2	2	99	8:1	14
2	THF	1	99	11:1	25
3	toluene	1	97	10:1	30
4	hexane	12	55	12:1	11

[a] The reaction was performed using **1a** (1.0 equiv), aryllead compound **2b** (3.0 equiv), and brucine (10 equiv) at rt. Refer to Scheme 3. For experimental details, see Supporting Information. [b] Yields are of isolated, purified **3b**. [c] (*R*,*R*)-**3b** is the major enantiomer.

Table 4. Effect of Metallation of **1a** and Additive in the Asymmetric Coupling with **2a**[a]

entry	M	brucine (equiv)	additive	conditions (°C, h)	yield (%)[b] **3a**	yield (%)[b] **4a**	ee (%) **3a**	ee (%) **4a**
1	**1a**	2.0	−	rt, 12	92	−	40	−
2	**1a**	3.0	−	−20, 1	−	8	−	47
3	**1b**	3.0	−	−20, 2	22	25	60	52
4	**1c**	3.0	−	−20, 1	11	8	64	54
5	**1d**	3.0	−	−20, 1	12	15	58	54
6	**1a**	3.0	MS 4 Å, 0.3 g/mmol	−20, 16	64	8	63	56
7	**1a**	3.0	MS 13X, 0.3 g/mmol	−20, 16	47	6	62	56
8	**1a**	6.0	MS 4 Å, 1.5 g/mmol	−20, 24	99	−	61	−
9	**1a**	2.0	MS 4 Å, 1.5 g/mmol	−20, 21	88	7	64	48
10	**1a**	1.0	MS 4 Å, 1.5 g/mmol	−20, 21	75	20	66	58
11	**1a**	0.2	MS 4 Å, 1.5 g/mmol	−20, 28	40	30	61	61

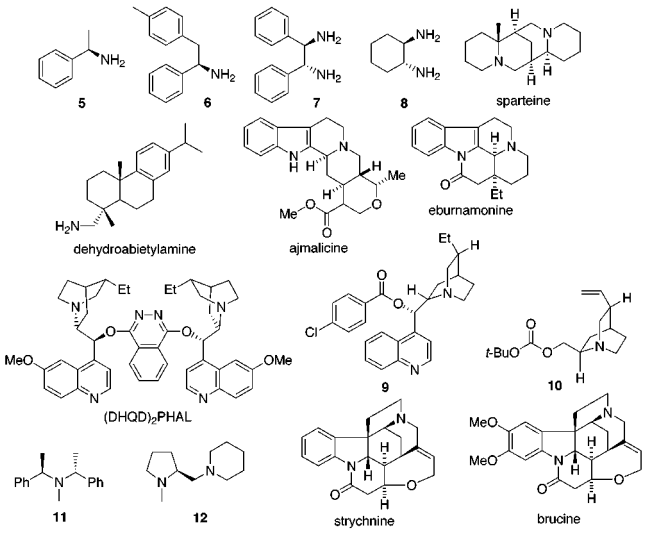
[a] The reaction was performed using **1a**−**1d** (1.0 equiv), aryllead compound **2a** (2.5 equiv), and brucine with or without additive in toluene. For M, refer to Scheme 3. For experimental details, see Supporting Information. [b] Yields are of isolated, purified products.

effectively at the *ortho*-position of phenols[18] and anilines[19] by simple metallation of the corresponding hydroxy and amino groups.

Phenol Coupling: Results and Discussion

Amine Survey. Pinhey suggested that the coupling reaction of phenols with aryllead triacetates is facilitated by the participation of excess pyridine or analogous bases in $CHCl_3$.[14] Thereafter, Barton carefully optimized the reaction conditions, particularly for the use of aryllead compounds that incorporated electron-rich aryl groups.[13] Our initial plan was guided by a reconsideration of an alternative base additive that could lead to the future discovery of a chiral analogue, with a goal of efficient asymmetric synthesis. We started with a search regarding the efficient synthesis of 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol (**3a)** by this ligand coupling using chiral amines instead of pyridine, since chiral phenol **3a** has been demonstrated to be an effective chiral auxiliary in the diastereoselective aldol[20a] and Mannich-type reactions[20b,c] of the corresponding chiral acetate. Thus, the coupling reaction of 3,5-dimethylphenol (**1a**) with 2-isopropylphenyllead triacetate (**2a**)[21] was carried out in the presence of various amines (Scheme 3 and Table 1). The rate-enhancing effect was moderate with a primary amine (entry 1), but less efficient with a secondary amine (entry 2) or tertiary amines, including *i*-Pr_2NEt and NEt_3 (entries 3 and 4). Surprisingly, this process using tertiary amines such as DABCO or quinuclidine exhibited good-to-excellent reactivity and high *dl*-selectivity (entries 5 and 6).[22,23] These results indicate that conformationally restricted amines may be useful for the rate enhancement.

We next investigated an asymmetric version of this process using optically active bases (Table 2). The use of bidentate amines led to slower reactions and incomplete consumption of starting phenol **1a** (entries 3−5, 7, 8, and 16). Poor yields were also obtained when quinuclidine derivatives with an oxygen functional group at the β-position were used (entries 9, 10, 13, and 14). In contrast, brucine, which has a conformationally restricted tertiary amine moiety, was essential to achieve rate enhancement in addition to high diastereoselectivity. Moreover, we obtained the best enantiomeric excess (ee) thus far (entries 12 and 18).[24] Despite the structural resemblance of strychnine to brucine, use of the former gave a lower yield as well as a lower ee (entry 17).



Optimization of Reaction Conditions. With the superior enantioselectivity exhibited by the combination of phenol **1a**,

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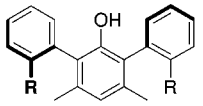
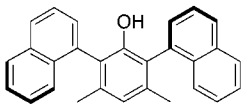
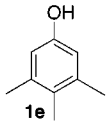
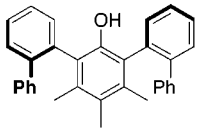
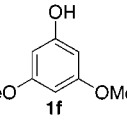
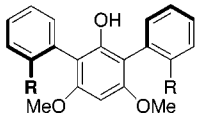
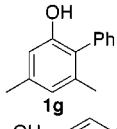
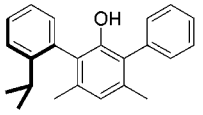
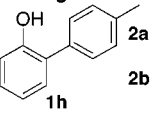
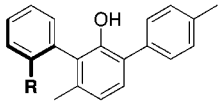
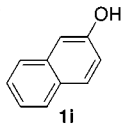
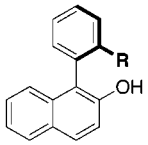
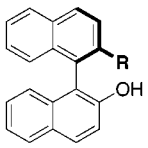
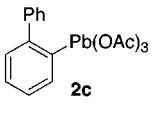
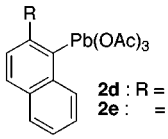
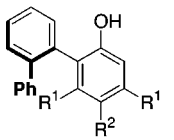
Table 5. Asymmetric Ligand Coupling With Various Arylleads[a]

entry	phenol	aryllead	conditions[b] (°C, h)		major coupling product	yield (%)[c] (*dl*:*meso*)	ee (%)[d] (config)[e]
1	**1a**	**2a**	-20, 21	**3a** (R = *i*-Pr)		99 (>99:1)	61 (*R*,*R*)
2	**1a**	**2b**	-20, 28	**3b** (R = Me)		>99 (13:1)	49 (*R*,*R*)
3	**1a**	**2c**	-20, 52 0, 12 rt, 24	**3c** (R = Ph)		68[h] (>99:1)	83
4	**1a**	**2d**	-20, 28	**3d**		>99 (2.0:1)	51
5	 **1e**	**2c**	-40, 120	**3e**		80[h] (>99:1)	87
6	 **1f**	**2a**	-40, 44 -20, 28	**3f** (R = *i*-Pr)		82 (>99:1)	54
7		**2c**	-40, 35 -20, 28 0, 17 rt, 24	**3g** (R = Ph)		55[h] (6.9:1)	93
8[f]	 **1g**	**2a**	-40, 24	**3h**		86	46
9[f]	 **1h**	**2a**	-40, 72	**3i** (R = *i*-Pr)		99	85
10[f]		**2b**	-40, 24	**3j** (R = Me)		85	75
11[g]	 **1i**	**2a**	-40, 10	**3k** (R = *i*-Pr)		86	77
12[f]		**2c**	-40, 48	**3l** (R = Ph)		83	89 (*R*)
14[f]		**2d**	-40, 6	**3m** (R = H)		99	35
15[f]		**2e**	-40, 4	**3n** (R = Me)		99	20

[a] Unless otherwise specified, reactions were performed using lithiated phenol (1 equiv), aryllead (2.5 equiv), MS 4 Å (3 g/mmol), brucine (6 equiv) in toluene. [b] All these reactants were mixed at −78 °C and reacted under each reaction condition(s). For experimental details, see Supporting Information. For entries 3, 6, and 7, reaction temperature was gradually increased as specified. [c] Of isolated, purified major coupling product. [d] Enantiomeric excess of phenols, which was determined by chiral HPLC analysis. [e] The absolute configuration of the major enantiomer, which was determined in comparison with that in the literature **3a**−**b**: ref. 20d: **3l**: ref. 38. Others are not assigned. [f] aryllead:brucine = 1.25:3 equiv. [g] aryllead:brucine = 1:1 equiv. [h] Mono-coupling products were also obtained (entry 3, **4b**, 26%, 38% ee; entry 5, **4c**, 16%, 70% ee; entry 7, **4d**, 25%, 29% ee).


2c


2d : R = H
2e : = Me


4b : R^1 = Me, R^2 = H
4c : R^1 = Me, R^2 = Me
4d : R^1 = MeO, R^2 = H

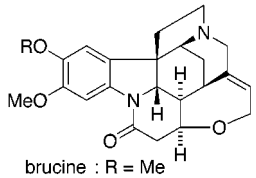
2-methylphenyllead triacetate (**2b**), and brucine (Table 2, entry 12), a study was initiated to survey solvent effects for this reaction (Table 3). The use of solvents such as CH_2Cl_2, THF, and toluene gave comparable yields of 3,5-dimethyl-2,6-bis(2-methylphenyl)phenol (**3b**) (entries 1−3); however, the reaction in hexane gave a lower yield, presumably due to the poor solubility of brucine (entry 4). Among the solvents examined, toluene gave the highest ee (entry 3).

To illustrate the effect of acetyl groups of arylleads on the enantioselectivity, 2-isopropylphenyllead tribenzoate (**13**) was prepared from lead tetrabenzoate[25] by the procedure described by Pinhey.[21c] The reaction between aryllead tribenzoate **13** and

(18) (a) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943. See also ref 8n.
(19) Saito, S.; Kano, T.; Ohyabu, Y.; Yamamoto, H. *Synlett* **2000**, 1676.
(20) (a) Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3378. (b) Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891. (c) Saito, S.; Hatanaka, K.; Yamamoto, H. *Tetrahedron* **2001**, *57*, 875. For preliminary preparation of **3a**,**b**, see: (d) Saito, S.; Kano, T.; Hatanaka, K.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5651.
(21) (a) Bell, H. C.; Kalman, J. R.; Pinhey, J. T. *Aust. J. Chem.* **1979**, *32*, 1521. (b) Kozyrod, R. P. Morgan, J.; Pinhey, J. T. *Aust. J. Chem.* **1985**, *38*, 1147. For the preparation of aryllead compounds **2a**−**e**, see: (c) Morgan, J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 715.

(22) The diastereoselectivity (*dl*:*meso*) was unambiguously ascertained by ^{1}H NMR and HPLC analysis. See ref 20d.

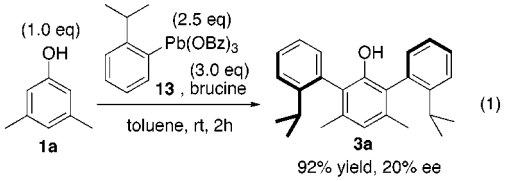
Table 6. Effect of Substituent on Brucine in the Asymmetric Coupling of **1a** with **2a**[a]



entry	brucine derivative	yield (%)[b] 3a	yield (%)[b] 4a	ee (%) 3a	ee (%) 4a
1	brucine	99	–	61	–
2	**14**	86	–	60	–
3	**15**	38	33	60	75

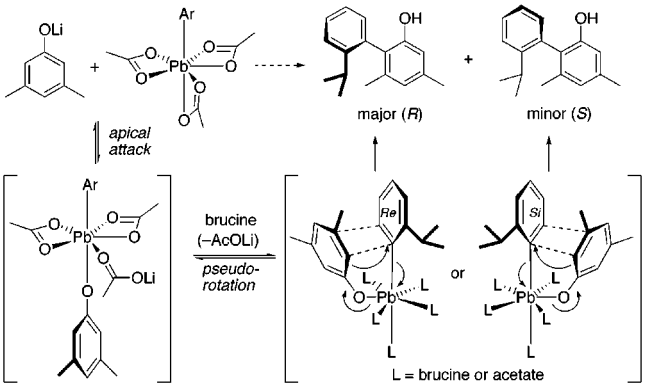
[a] The reaction was performed using **1b** (1.0 equiv), aryllead compound **2a** (2.5 equiv), and brucine derivative (3−6 equiv) in the presence of MS 4 Å in toluene at −20 °C. Refer to Scheme 3. For experimental details, see Supporting Information. [b] Of isolated, purified product.

phenol **1a** using brucine gave a comparable yield of **3a**, albeit with a lower enantioselectivity (eq 1).



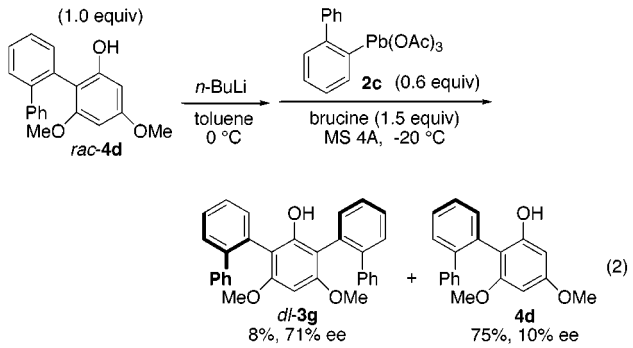
When the reaction was performed at a lower temperature (−20 °C), only mono-coupling product **4a** was obtained in a low yield, albeit with slightly higher enantioselectivity (Table 4, entry 2). To accelerate the reaction rate, we next examined the effect of the metallation of phenols (Table 4). With lithium phenoxide, prepared by treatment of phenol **1a** with *n*-BuLi at 0 °C in toluene, di-coupling product **3a** was obtained in a higher yield under similar conditions (entry 3). This may be due not only to the higher reactivity of the metal phenoxide with aryllead triacetates but also to the decreased amount of byproduct, acetic acid, which might concomitantly form a salt with brucine, which subsequently retards reaction rates. An even more significant problem is that another equivalent of acetic acid is formed during the second coupling. Attempts to remove acetic acid by the known inclusion effect of molecular sieves (4 Å or 13X) resulted in higher yields (entries 6 and 7). Finally, we found that the coupling reaction reached completion faster using an excess (6 equiv) amount of brucine (entry 8). Despite lower conversions and slower reaction rates, no decrease of enantioselectivity was achieved using smaller quantities of brucine (entries 9−11). These results indicate that a catalytic amount of brucine could facilitate the reaction, and in fact an improved turnover number (5.5) was realized using 0.2 equiv of brucine (entry 11).

Scheme 4



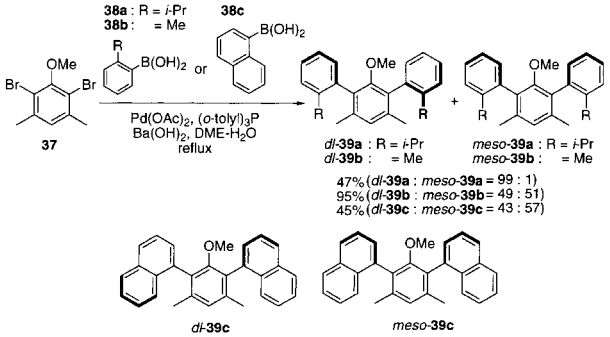
Reaction Scope. The procedure described above was extended to the synthesis of various chiral phenols (Table 5). In general, the coupling of phenols with aryllead triacetates proceeded in high yield with moderate-to-high enantioselectivity, along with excellent diastereoselectivity. In particular, (2-phenyl)phenyllead triacetate (**2c**) was generally suitable in terms of high ee (entries 3, 5, 7, and 12). Subsequent simple recrystallization from cyclohexane or hexane led to enantiomerically pure phenols **3a**, **3c**, and **3e**.

The kinetic resolution of mono-arylated phenols was observed in the second coupling leading to terphenols. For instance, the coupling of 3,5-dimethoxyphenol (**1f**) with aryllead **2c** gave di-coupling product **3g** with high enantiomeric excess (93% ee), along with mono-coupling product **4d** with 29% ee (entry 7). Further investigation indicated that the coupling of racemic mono-arylated phenol **4d** with aryllead **2c** gave di-coupling product **3g** with 71% ee in 8% yield, demonstrating kinetic resolution despite the low conversion (eq 2).



Brucine Derivatives. Strychnine, which lacks methoxy substituents on the aromatic ring, is a structural analogue of brucine. Because the coupling reaction with strychnine gave a lower enantioselectivity than that with brucine (Table 2, entries 17 and 18), we speculated that the methoxy group on the aromatic ring could affect enantioselectivity. Therefore, further studies to improve the enantioselectivity were carried out using two other brucine derivatives (Table 6). Benzyloxy-substituted

(23) 2,6-Dibromo-3,5-dimethylanisole (**37**) and boronic acids **38a**−**c** were subjected to Suzuki coupling to give the corresponding terphenyl adducts **39a**−**c** with moderate yields and diastereoselectivities as shown below.



(24) The ee % of each adduct was determined by chiral HPLC analysis.
(25) Hey, D. H.; Stirling, C. J. M.; Williams, G. H. *J. Chem. Soc.* **1954**, 2747.

Scheme 5

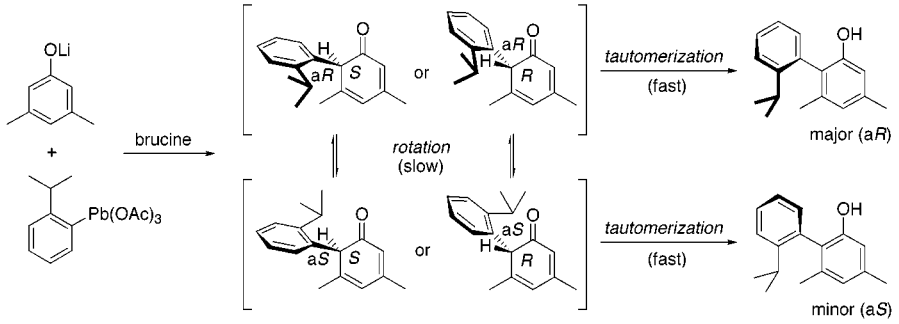
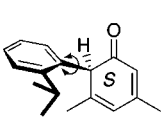
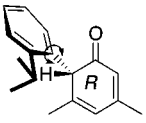
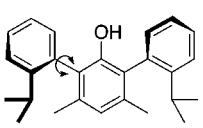
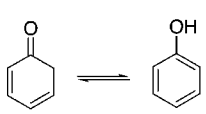


Table 7. Calculated Rotational Barrier[a]

rotation direction				
to the methyl group ΔG (kcal/mol)	17.7	16.5	34.9	energy barrier ΔG = 6 kcal/mol[27a]
to the C=O group ΔG (kcal/mol)	15.3	11.2	38.1	

[a] These values were calculated by AM1 semiempirical computations, which were carried out using the Cerius 2 program (ver. 2.38) with full geometry optimization.

brucine **14** had little effect on the enantioselectivity of the reaction between lithium phenoxide **1b** and aryllead **2a** (entry 2). In contrast, the reaction with silyl-protected brucine **15** resulted in incomplete conversion of the starting substrate but an increase in the ee of the mono-coupling product **4a** (entry 3).

Plausible Mechanistic Model. Since brucine plays a critical role in the high diastereo- and enantioselectivity, it presumably coordinates to the Pb center to promote ligand coupling. With this in mind and as suggested by Pinhey[26a−c] and Moloney,[26d,e] a plausible mechanism for asymmetric ligand coupling can be proposed (Scheme 4).

First, the lithium phenoxide coordinates to an apical position of lead, and the resulting lithium acetate might undergo ligand exchange with brucine. Subsequently, the configuration and conformation of this complex are thought to be controlled by the steric effect of brucine during pseudorotation. Finally, oxidative coupling occurs to give (*R*)-**4a** as the major isomer.

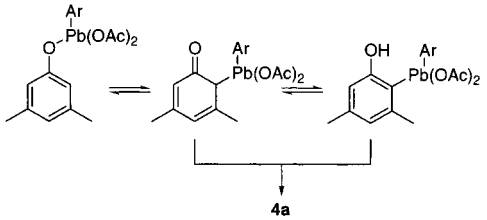
The formation of a C−C bond between a phenol and an aryllead, as a phenyl cation equivalent, initially affords α-substituted dienones with a chiral center at their α-positions (Scheme 5). We envisioned that the axial chirality of the resulting phenol is not transferred from this central chirality of the initially formed dienone but rather arises from the chiral axis linking the dienone and its aryl group. The validity of this mechanism which involves the tautomerization of an axially chiral ketone to the corresponding phenol with no loss of axial chirality was demonstrated by comparing several energy barriers of rotation. These were determined by semiempirical calculations (AM1) as well as some calculated results in the literature.[27] Since the rotational barrier around the chiral axis at the α-position of the ketone (minimum value: >11.2 kcal/mol, for rotation in the direction of C=O, see Scheme 5 and Table 7) is much higher than the energy barrier between phenol and 2,4-cyclohexadien-1-one (ca. 6 kcal/mol),[27a] tautomerism of a dienone to the phenol is likely to be much faster than rotational isomerism. In this mechanism, whether the initially formed central chirality is *S* or *R* is not important for inducing axial chirality. Rather, a (pseudo)axial chirality appended primarily on the sp^3 carbon should be translated accurately into a chiral axis on the sp^2 carbon, either a*S* or a*R*, although other possible chiral transfer pathways could not be ruled out.[28]

On the basis of the above consideration and the high diastereoselectivity (*dl* over *meso*) generally observed for dicoupling products, the second coupling might be impaired by steric constraints between the *ortho* substituents of the two arene

(26) (a) Morgan, J.; Hambley, T. W. Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2173. A free-radical process seems highly unlikely, see: (b) Hambley, T. W.; Holmes, R. J.; Parkinson, C. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1927. (c) Morgan, J.; Parkinson, C. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3361, and references therein. (d) Buston, J. E. H.; Compton, R. G.; Leech, M. A.; Moloney, M. G. *J. Organomet. Chem.* **1999**, *585*, 326. Ligand influence on the reactivity of aryllead triacetates: (e) Moloney, M.; Oaul, D. R.; Prottey, S. C.; Thompson, R. M.; Wright, E. *J. Organomet. Chem.* **1997**, *534*, 195.

(27) Energy barrier: between phenol and 2,4-cyclohexadien-1-one, see: (a) Shiner, C. S.; Vorndam, P. E.; Kass, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 5699; between cyclohexen-1-ol and cyclohexanone, see: (b) Zhang, X.-M. *J. Org. Chem.* **1998**, *63*, 5314.

(28) Another possibility would be a tautomerization of the aryloxylead to a 2,4-cyclohexadienone with lead in the 6-position followed by subsequent reductive elimination, or by further tautomerization−reductive elimination. See also below. In fact, the *C*-bound, rather than *O*-bound, lead was isolated as a single-crystal structure of a ketone enolate, see: Morgan, J.; Buys, I.; Hambley, T. W.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans 1* **1993**, 1677. One of the reviewers suggested that the effects of ligands and additives could be understood in terms of promoting the tautomerization equilibrium or the reductive elimination.



Scheme 6

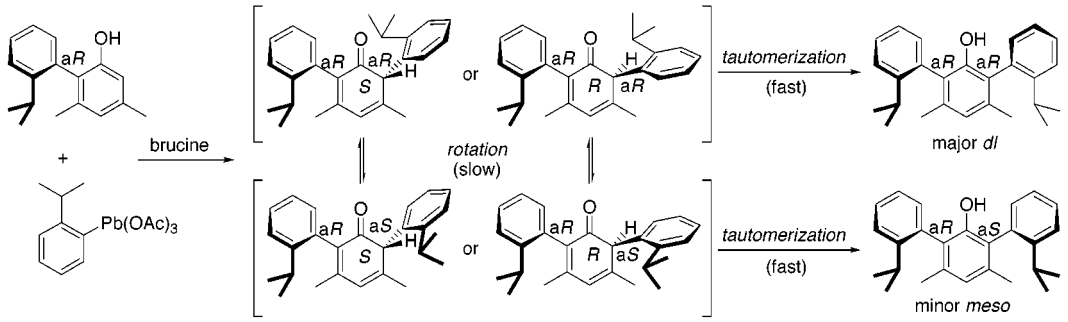
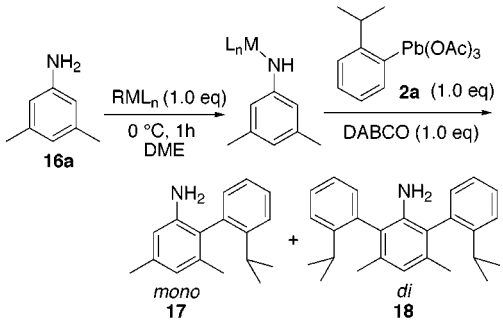
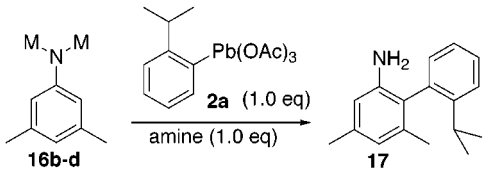


Table 8. Coupling Reactions of Aryllead with Metal Anilides



		yield (%)	
entry	RML_n	*mono* (**17**)	*di* (**18**)
1	BuLi	10−20	−
2	*t*-BuMgCl	55−66	4−10
3	MeMgCl	24	2
4	MeMgBr	<5	−
5	MeMgI	<5	−
6	MeZnCl	<5	−

Table 9. Coupling Reactions of Aryllead with Dimetal Anilides



	dimetal anilide	M	amine	solvent	% of yield **17**[a]
1	**16b**	MgCl	quinuclidine	toluene	28 (8)
2	**16c**	Li	brucine	THF	14
3	**16d**	TMS	quinuclidine	toluene	0

[a] Yield in the parenthesis indicates the yields of di-coupling product **18**.

rings in aryllead and mono-arylated products to give *dl*-terphenols (Scheme 6). However, the steric effect of brucine is nonnegligible in the second coupling, since in some cases kinetic resolution proceeded.

Aniline Coupling: Results and Discussion

Effect of Metalation. We were next interested in further developing this coupling method using aryllead triacetates to achieve *C*-(*ortho*-)arylation of anilines. Barton pointed out that no reaction occurred between amines and organolead derivatives alone.[15] We speculated that anilines alone could not undergo ligand exchange with an acetoxy group of aryllead triacetates. Thus, our initial plan was to investigate the metallation of aniline nitrogen, which might promote effective ligand exchange and subsequent arylation with aryllead triacetate (Table 8). Since not only the lithiation of phenols but also the use of DABCO or quinuclidine facilitates the aryl−aryl coupling of aryllead triacetate with phenols, we first tested the effect of lithiation and a base additive on aniline coupling. The reaction of 2-isopropylphenyllead triacetate **2** with the lithium anilide (which was prepared from 3,5-dimethylaniline **16a** and *n*-BuLi) in the presence of DABCO in DME afforded only a small amount of the desired *ortho*-arylated product **17** (Table 8, entry 1). We next examined a magnesium anilide that would be expected to promote the ligand exchange by abstraction of an acetoxy group due to the greater Lewis acidity of magnesium. Treatment of magnesium anilide, prepared in situ by the reaction of aniline **16a** with *t*-BuMgCl, with aryllead **2a** gave aniline **17** in 55−65% yield, along with di-arylated aniline **18** (entry 2). In contrast, metallating agents other than *t*-BuMgCl led to a significant decline in yield (entries 3−6).

To achieve more effective ligand exchange, the effect of dimetallated anilines, which would be expected to be more nucleophilic, was examined (Table 9). Dimagnesium, dilithium, and disilyl anilides **16b**−**d** were prepared as described in the literature.[29,30] Disappointingly, this dimetallation strategy proved to be less effective, even though dimagnesium anilide **16b** had higher potential than the others (Table 9, entry 1).

Optimization. With the superb productivity exhibited by the combination of *t*-BuMgCl (1 equiv) and aniline **16a** (1 equiv), we next examined the solvent effects. The use of Et_2O (**17**, 43%; **18**, 5%) or dioxane (**17**, 39%; **18**, 4%) gave rather lower yields, while the use of other solvents, such as DME (**17**, 55−66%; **18**, 4−10%), THF (**17**, 55−66%; **18**, 2−10%), *t*-BuOMe (**17**, 55−70%; **18**, 9−12%), or toluene (**17**, 55−66%; **18**, 2−10%), led to comparable yields. Toluene was eventually chosen as a suitable solvent with regard to both productivity and reproducibility.

Finally, we found that the mixing ratio of the starting substrates (aryllead **2a**:aniline **16a**:*t*-BuMgCl:DABCO = 1.0:1.3:1.3:1.0) was even more critical for high productivity. The mono-arylated product **17** was obtained in 85−88% yield based on the initial amount of Pb reagent under these optimal conditions. Quinuclidine, which has a structure analogous to that of DABCO, was also examined as a base to give **17** in a similar yield. Even more interesting is the fact that the reaction proceeded smoothly without a base to give **17** in 74% yield. This result indicates that the reaction could be autocatalyzed by primary amines that were generated as the reaction proceeded.

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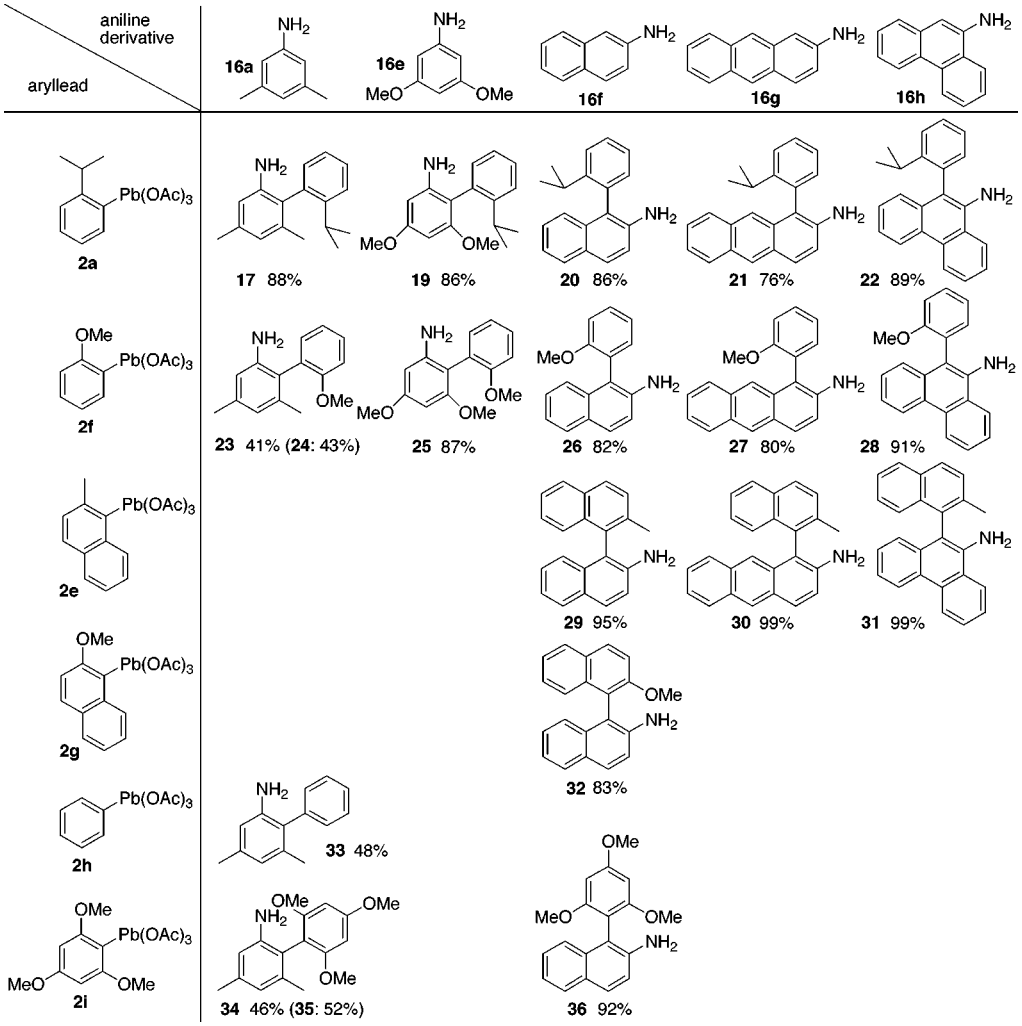
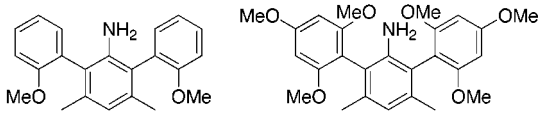
(30) Abel E. W.; Willey, G. R. *J. Chem. Soc.* **1964**, 1528.

Table 10. Coupling of Anilines With Aryllead Triacetate[a,b]



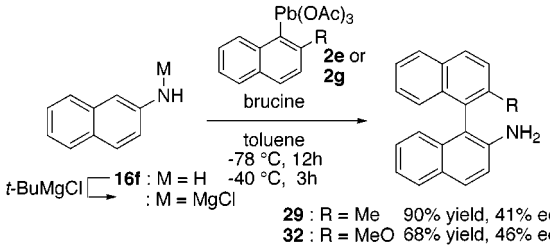
[a] The reaction was performed using aniline (1.3 equiv), *t*-BuMgCl (1.3 equiv), aryllead (1.0 equiv) in toluene. The yield in parenthese is of dicoupling product. For experimental details, see Supporting Information. [b] Yields are of isolated, purified product.



Reaction Scope. Given the optimal reaction conditions, a wide variety of *ortho*-arylanilines were readily synthesized, as shown in Table 10. This new reaction is characterized by several features: (1) Various aromatic amines were selectively arylated at the *ortho* position. (2) The reactive arylleads with electron-donating groups on their aromatic rings gave generally high yields. (3) *o*-Methoxyarylleads **2f** and **2i**[13] showed novel reactivity with **16a**, and the second *ortho* arylation proceeded further to give significant amounts of the di-coupling products **24** and **35**, respectively. (4) In contrast, the reaction of phenyllead triacetate **2h** was sluggish due to its poor reactivity, resulting from the greater electron-deficient nature of the aromatic ring.[14]

Asymmetric Coupling. Since biarylamines bearing axial chirality are readily obtained by this aryl−aryl coupling reaction, an enantioselective version of this reaction was investigated. The use of brucine is essential for the asymmetric coupling

Scheme 7



reaction of phenols with aryllead compounds, and this method was applied to the synthesis of chiral aromatic amines (Scheme 7). When brucine was used instead of DABCO, the coupling reaction of β-naphthylamine **16f** with 2-methylnaphthyllead triacetate **2e** or 2-methoxynaphthyllead triacetate **2g** proceeded even at a lower temperature (−78 to −40 °C) to give the desired axially chiral biaryls **29** (41% ee) and **32** (46% ee). These results indicate that brucine participates in the asymmetric process of

C−C bond formation, and therefore the coordination of brucine to Pb may accelerate the reaction rate. However, the enantioselectivity might be lowered by concomitant autocatalyzation with primary amines that were generated as the reaction proceeded.

Conclusions

This work describes a new method for preparing a variety of optically active biphenyls and terphenyls with axial chirality by the coupling of phenols with aryllead compounds. Quinuclidine, which acts as a base ligand on a lead center, was shown to promote the ligand coupling. This observation was successfully extended to the use of brucine, which also has a conformationally restricted tertiary amine moiety, to give the desired axially chiral phenols with moderate-to-high enantioselectivity and excellent diastereoselectivity. This new method can be applied to the sterically hindered substrates, which are difficult to be cross-coupled by transition-metal catalysts.

Magnesium anilides, prepared from anilines with *t*-BuMgCl, showed great synthetic potential to achieve the *C*-arylation of anilines with aryllead triacetates in the presence of tertiary amines such as DABCO and quinuclidine. In this reaction, major products are mono-arylated anilines at their *ortho* positions, which are directly accessible from various aromatic amines. This is in contrast to the preferential *ortho,ortho*-diarylation of phenols with aryllead derivatives. This method is also advantageous with regard to the substitution pattern, since anilines are otherwise prone to electrophilic substitution at their para positions. Further examination indicated that the use of less than 1 equiv of *t*-BuMgCl is critical for producing mono-arylation, since mono-arylated anilines should not be further metallated under these conditions, which would result in desirable retardation of the second coupling. However, highly reactive lead reagents such as 2-methoxyphenyllead triacetate and 2,4,6-trimethoxyphenyllead triacetate sometimes gave considerable amounts of doubly arylated products. The significance of axially chiral anilines is manifold, since ligation of an aniline structure is frequently found in metal catalysts that have recently been revolutionizing selective transformations.[31−37]

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Supporting Information Available: Spectral and analytical data for all new compounds, and typical experimental procedures for the coupling of phenols and anilines (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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