Asymmetric Coupling of Phenols with Arylleads

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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] but also chiral metal catalysts[2] and artificial helical polymers.[3] Despite a broad spectrum of classical[4] and modern[5] procedures for the chemical connection of 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 of great importance. We report here the first example of the diastereo- and enantioselective direct coupling of aryllead compounds with phenol derivatives.

Pinhey suggested that the coupling reaction of phenols with aryllead triacetates[7] is facilitated by the participation of excess pyridine (ca. 10 equiv) or analogous bases in $CHCl_3$.[8] Thereafter, Barton carefully optimized the reaction conditions, particularly for the use of aryllead compounds which incorporate electron-rich aryl groups.[9] Our initial plan was guided by a reconsideration of an alternative base additive which could open the way to the future discovery of a chiral analogue, with a goal of the efficient asymmetric synthesis. Since 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol (**3a**)[10] has been demonstrated to be an effective chiral auxiliary in the diastereoselective aldol reaction of the corresponding chiral acetate,[10a] we first investigated the synthetic efficiency of **3a** with several different bases (toluene, room temperature, 2 h) (Scheme 1). The rate-enhancing effect was most prominent with at least 3 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) or quinuclidine (**3a**, 80% and 95%, respectively) but less efficient with primary amines (*i*-$PrNH_2$, **3a**, 75%; **4**, 7%). An attempt to use other tertiary amines, including NEt_3 and *i*-Pr_2-NEt (**4**, 11% and 10%, respectively), and secondary (*i*-Pr_2NH; **4**: 31%) as well as bidentate amines (*trans*-1,2-diphenyldiaminoethane and *trans*-1,2-diaminocyclohexane; **4**, 7% and 5% yield, respectively) proved totally fruitless. This process using DABCO or quinuclidine exhibited high *dl*-selectivity (>99% de); in comparison, Suzuki coupling was carried out and gave consistently lower *dl*-selectivities as well as lower chemical yields.[11,12]

Scheme 1

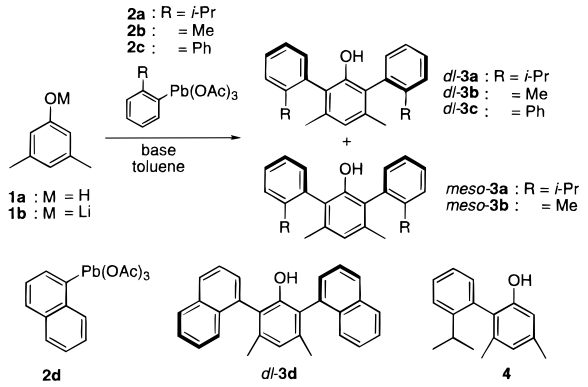
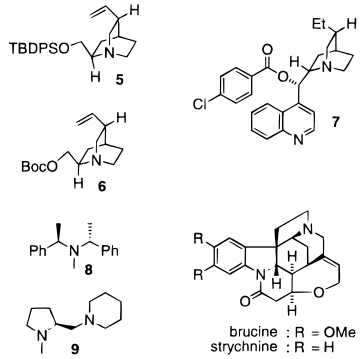


Table 1. Asymmetric Coupling of **1a** with **2a** in the Presence of Chiral Base[a]

entry	base	yield (%)[b]	ee (%)[c]	entry	base	yield (%)[b]	ee (%)[c]
1	**5**	16[d]	0	5	**9**	3[d]	0
2	**6**	8[d]	10	6	strychnine	32[e]	20
3	**7**	14[d]	4	7	brucine	92[e]	40
4	**8**	2[d]	4				

[a] Reactions were carried out using **2a** (2.5 equiv), **1** (1 equiv), and a base (3 equiv) in toluene at room temperature for 3 h. [b] Unless otherwise specified, of isolated, purified dicoupling product **3a**. [c] Determined by HPLC analysis. [d] Of isolated, purified monocoupling product **4**. [e] The ratio of *dl* and *meso* products = >99:<1.



On the basis of the structural features of quinuclidine, we next elucidated the potential for an asymmetric version of this process using optically active bases (Table 1). We found that brucine was essential to achieve rate enhancement in addition to high diastereoselectivity. Moreover, we obtained the best enantiomeric excess (ee) so far (40% ee).[13] The participation of even a small amount of H_2O retarded the rate, as exemplified by the use of brucine hydrate. Protocols which used toluene were preferable, although the use of other solvents also gave reasonable yields

(1) Evans, D. A.; Wood, M. R.; Trotter, W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2700. (b) Nicolaou, K. C.; Natarajan, S.; Li, H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N. C.; Takayanagi, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2708. (c) Meyers, A. I.; Willemsen, J. J. *Chem. Commun.* **1997**, 1673. (d) Chau, P.; Czuba, I. R.; Rizzacasa, Bringmann, G.; Gulden, K.-P.; Schäffer, M. *J. Org. Chem.* **1996**, *61*, 7101.

(2) (a) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin Heidelberg, in press. (b) Noyori, R., Ed. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.

(3) See ref 7 in Supporting Information.

(4) (a) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, N.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(5) See ref 8 in Supporting Information.

(6) See ref 9 in Supporting Information.

(7) (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**−**d**, see: (c) Morgan, J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 715.

(8) (a) Bell, H. C.; Pinhey, J. T.; Sternhell, S. *Aust. J. Chem.* **1979**, *32*, 1551. (b) Pinhey, J. T. *Aust. J. Chem.* **1991**, *44*, 1353. (c) Pinhey, J. T. *Pure Appl. Chem.* **1996**, *68*, 819.

(9) Barton, D. H. R.; Donnelly, D. M. X.; Guiry, P. J.; Finet, J.-P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2921.

(10) (a) Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3378. For preliminary preparation of **3a**,**b**, see: (b) Saito, S.; Kano, T.; Hatanaka, K.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5651.

(11) 2,6-Dibromo-3,5-dimethylanisole (**17**) and boronic acids **18a**−**c** were subjected to Suzuki coupling to give the corresponding terphenyl adducts **19a**−**c** with moderate yields and diastereoselectivities. See Supporting Information and also ref 10b.

(12) The diastereoselectivity (*dl*:*meso*) was unambiguously ascertained by ^1H NMR and HPLC analysis. See ref 10b.

(13) The ee % of each adduct was determined by chiral HPLC analysis. The rather low yield by slow reaction with strychnine is probably due to its insolubility in toluene.

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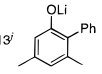
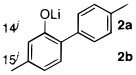
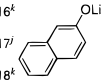
Table 2. Asymmetric Ligand Coupling with Various Arylleads[a]

entry	lithium phenoxide	aryllead	conditions[b] (°C, h)	major coupling product	yield (%)[c] (*dl*:*meso*)	ee (%)[d] (config)[e]	ee (%)[f] (yield %)
1	**1b**	**2a**	-20, 21	**3a** (R = *i*-Pr)	99 (>99:1)	61 (*R*,*R*)	99 (51)
2[g]	**1b**	**2a**	-20, 21	**3a**	88[l] (>99:1)	64 (*R*,*R*)	
3[h]	**1b**	**2a**	-20, 21	**3a**	75[l] (>99:1)	66 (*R*,*R*)	
4[i]	**1b**	**2a**	-20, 28	**3a**	40[l] (>99:1)	61 (*R*,*R*)	
5	**1b**	**2b**	-20, 28	**3b** (R = Me)	>99 (13:1)	49 (*R*,*R*)	
6	**1b**	**2c**	-20, 52 0 , 12 rt, 24	**3c** (R = Ph)	68[l] (>99:1)	83	>98 (77)
7	**1b**	**2d**	-20, 28	**3d**	>99 (2.0:1)	51	
8		**2c**	-40, 120	**10**	80[l] (>99:1)	87	>99 (87)
9[g]		**2c**	-40,3 0, 12	**10**	93[l] (>99:1)	86	
10		**2a**	-40, 44 -20, 28	**11** (R = *i*-Pr)	82 (>99:1)	54	
11		**2c**	-40, 35 -20, 28 0, 17 rt, 24	**12** (R = Ph)	55[l] (6.9:1)	93	
12[g]		**2c**	-40, 3 0, 32	**12**	49[l] (49:1)	93	
13[j]		**2a**	-40, 24	**13**	86	46	
14[j]		**2a**	-40, 72	**14a** (R = *i*-Pr)	99	85	
15[j]		**2b**	-40, 24	**14b** (R = Me)	85	75	
16[k]		**2a**	-40, 10	**15** (R = *i*-Pr)	86	77	
17[j]		**2c**	-40, 48	**16** (R = Ph)	83	89 (*R*)	
18[k]		**2c**	-40, 10	**16**	86	80 (*R*)	

[a] Unless otherwise specified, reactions were performed using lithiated phenol (1 equiv), aryllead (2.5 equiv), 4-Å molecular sieves (3 g/mmol), brucine (6 equiv) in toluene. [b] All these reactions were mixed at −78 °C and reacted under each reaction condition(s). For entries 6 and 9−12, reaction temperature was gradually increased as specified. [c] Of isolated, purified dicoupling product. [d] Enantiomeric excess of terphenyls, 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 10b; **16**, ref 18. Others are not assigned. [f] The yield and ee % of obtained crystals (entry 1) or filtrate (entry 6 and 8) after recrystallization from cyclohexane (entries 1 and 6) or hexane (entry 8) at room temperature. [g] Aryllead:brucine = 2:2 equiv. [h] Aryllead:brucine = 2:1 equiv. [i] Aryllead:brucine = 2:0.2 equiv. [j] Aryllead:brucine = 1.25:3 equiv. [k] Aryllead:brucine = 1:1 equiv. [l] Monocoupling products were also obtained (entry 2, 7%, 48% ee; entry 3, 20%, 58% ee; entry 4, 30%, 61% ee; entry 6, 26%, 38% ee; entry 8, 16%, 70% ee; entry 9, 6%, 56% ee; entry 11, 25%, 29% ee; entry 12, 43%, 49% ee).

despite a decline in ee values (CH_2Cl_2, 25% ee; THF, 24% ee). After screening various coupling conditions, we were pleased to find that not only the lithiation of phenols but also the use of molecular sieves (4 Å or 13×) accelerated the reaction rate.[14,15] Thus, coupling could be performed at lower temperatures (−40 to −20 °C), and we were successful in increasing the ee (**3a**, 99% yield, 61% ee). Fortunately, optically pure (*R*,*R*)-**3a** (>99% ee) was readily obtainable in 51% yield upon recrystallization from cyclohexane at room temperature.

To illustrate the scope of this asymmetric ligand coupling using brucine, a diverse set of lithiated phenols and arylleads was coupled (Table 2). High diastereoselectivity was consistently observed. Using less brucine gave inferior (entry 2, **3a**, 88%; **4**, 7%; **1a**, 5%) or comparable results (entries 9 and 12). (2-Phenyl)-

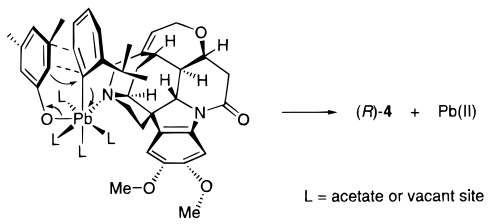


Figure 1.

phenyllead triacetate (**2c**) was generally suitable in terms of high ee (entries 6, 8, 9, 11, 12, 17, and 18). It is reasonable to suggest that the initial chirality has a nonnegligible influence on the rate of the diastereoselective second arylation (entries 2, 3, 6, 8, 9, 11, and 12).

Despite the lack of clear evidence, brucine might ligate to Pb metal, thereby inducing high enantio- and diastereoselectivity (Figure 1).[16] A substoichiometric (1 equiv) or catalytic (0.2 equiv) amount of brucine gave turnover numbers of 1.5 and 5.5, respectively (entries 3 and 4, Table 2).[17] The comparable ee (entries 1−4) also suggests that brucine makes identical complexes reversibly with Pb(IV) and Pb(II).

In summary, we have demonstrated a new approach to optically active aryl compounds with axial chirality that is applicable even to bulky aromatics. This method should be advantageous for several reasons. First, it enables bi- or terphenyl construction directly from phenols; i.e., it would obviate the need to prepare ArX, such as arylhalides or -triflates, which are frequently involved in conventional coupling events. Second, two aromatic nuclei could simultaneously be introduced to 3,5-disubstituted phenols, to give terphenyls with high diastereoselectivity. Third, it requirs only a simple operation involving the use of economically available brucine, to give ee values up to 93%.

Supporting Information Available: Preparation methods and characterization data for all new compounds and a comparison experiment involving Suzuki coupling (see ref 11) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) In a large-scale procedure, to a solution of phenol **1a** (6.10 g, 50.0 mmol) in toluene (650 mL) was added a 1.59 M hexane solution of *n*-BuLi (31.4 mL) at 0 °C under argon, and the mixture was stirred for 15 min. After the mixture was cooled to −78 °C, brucine (39.4 g, 100 mmol) [*Caution!* EXTREMELY POISONOUS (oral LD_{50} in rats = 1 mg kg^{-1}). Handle in well-ventilated hood only.], aryllead **2a** (50.4 g, 100 mmol) [*Caution!* Poisonous. Handle in well-ventilated hood only.] and 4-Å molecular sieves powder (150 g) were added sequentially. The mixture was stirred at −20 °C for 21 h and filtered through a Celite pad. The obtained cake was washed with CH_2Cl_2, and the filtrate was concentrated. The residue was purified by column chromatography, where nonpolar products initially came off the column (diethyl ether/hexane = 1/10 to 1/1 as the eluent) to give **3a** (15.6 g, 88%), **4a** (0.84 g, 7%), and **1a** (0.31 g, 5%), whereas brucine remained at almost the starting point of the column. The next eluent (Et_3N/MeOH = 1/10) allowed >90% recovery of brucine, which can be reused after being washed with 10% NH_4OH and subsequently with diethyl ether and dried (100 °C for 12 h at 3 mmHg).

(15) It is not yet possible to explain these effects on the rate acceleration. However, one reasonable explanation is that lithiation and the use of molecular sieves preclude the involvement of AcOH, which may retard the rate by intervening in the formation of lead phenoxides.

(16) This speculation is due to a mechanistic model proposed by Pinhey, in which pyridine would be bound to Pb to promote significant rate acceleration, see: (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.

(17) This interesting result may be improved by a more efficient catalysis which is now under investigation.

(18) Nishikiori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245.