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Acceleration of Arylzinc Formation and Its Enantioselective Addition to Aldehydes by Microwave Irradiation and Aziridine-2-methanol Catalysts

Antonio L. Braga,*[,†] Marcio W. Paixão,[†,‡] Bernhard Westermann,[‡] Paulo H. Schneider,[§] and Ludger A. Wessjohann*[,‡]

Universidade Federal de Santa Maria, Departamento de Química, 97105-900, Santa Maria RS, Brazil, Leibniz Institute of Plant Biochemistry, Bioorganic Chemistry, Weinberg 3, 06120 Halle, Germany, and Instituto de Química, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

albraga@quimica.ufsm.br

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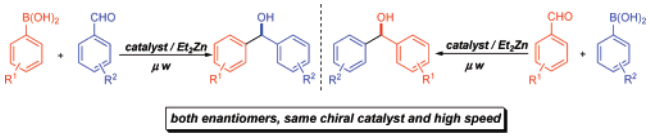
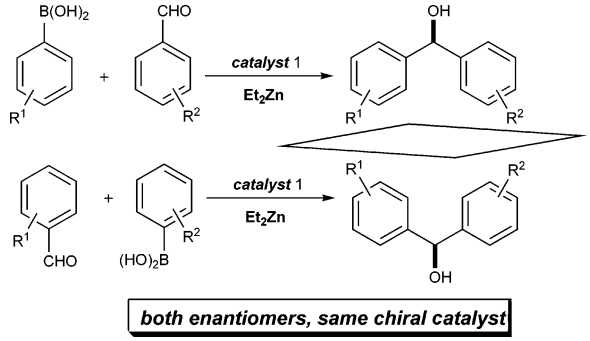


The formation and 2-amino alcohol catalyzed addition of arylzinc reagents from and with boronic acids, respectively, is drastically accelerated to a few minutes under microwave irradiation without loss of enantioselectivity (up to 98% ee). Of the amino acid derived catalysts tested, the conformationally restricted bulky substituted aziridine-2-methanols derived from serine show the best overall performance in the formation of diarylmethanols.

The enantioselective arylzinc addition to aldehydes in the presence of chiral ligands has received special attention since it gives access to chiral diarylmethanols, important precursors for pharmacologically and biologically important compounds.[1] Recently, an intriguing protocol was introduced by Bolm which takes advantage of boronic acids as source of the nucleophilic aryl species formed by a boron−zinc exchange reaction with diethylzinc.[2] This method allows the exploitation of a broader range of substituted aryl transfer reagents, since numerous arylboronic acids are readily available. The most relevant feature

SCHEME 1. Catalytic Arylation of Aldehydes with Arylboronic Acids



of this method is the selective access to both enantiomers of a given product by using one enantiomer of a chiral ligand, just by interchanging the reactive groups of reaction partners: boronic acid and aldehyde (Scheme 1). As reported previously, the same outcome can be realized by utilizing piperidine- and pyrrolidine derived ligands **1** and **2** (Figure 1), which exhibit inverted induction preference.[3]

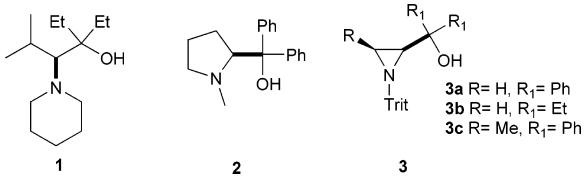


FIGURE 1. Successful ligands for the enantioselective aryl addition to aldehydes. Trit = trityl (triphenylmethyl).

For the system *p*-tolualdehyde/phenylboronic acid, ligand **1** gives the (*R*)-enantiomer in high selectivity. The reverse enantioselectivity can be observed with the five-membered ligand **2** (Table 1, entries 1 vs 2).

However, the procedure requires quite long reaction times, a serious drawback for automated parallel synthesis. Recent advances in microwave irradiation (μw) have greatly impacted many aspects of chemical synthesis, mainly transition-metal-catalyzed reactions such as asymmetric palladium-catalyzed allylic alkylations[4] and palladium-catalyzed cross-coupling reactions.[5] Very recently, it has been shown that organocatalytic

† Universidade Federal de Santa Maria.
‡ Leibniz Institute of Plant Biochemistry.
§ Universidade Federal do Rio Grande do Sul.

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TABLE 1. Catalytic Arylation of *p*-Tolualdehyde with Phenylboronic Acid[a]

entry	ligand (mol %)	*T* (°C)	yield[b] (%)	ee[c,d] (%)
1	**1** (20)	20	97	97 (*R*)
2	**2** (20)	0	95	94 (*S*)
3	**3a** (20)	20	96	96 (*S*)
4	**3b** (20)	20	97	98 (*S*)
5	**3c** (20)	20	96	17 (*S*)
6	**3a** (10)	20	97	96 (*S*)
7	**3a** (5)	20	95	91 (*S*)
8	**3a** (10)	0	94	96 (*S*)
9	**3a** (10)	60	96	80 (*S*)

[a] Reactions were performed on a 0.5 mmol scale with $PhB(OH)_2$ (2.4 equiv), Et_2Zn (7.2 equiv) in toluene (stirring at 60 °C for 12 h (time 1), then addtion of catalyst and aldehyde, with stirring for 12 h (time 2)). [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC on a Chiralcel OD column. [d] Absolute configuration assigned by correlation to literature data.[2]

TABLE 2. Microwave Irradition Assisted Arylations of *p*-Tolualdehyde with Phenylboronic Acid[a]

entry	ligand (mol %)	time 1[b]	time 2[b]	method[c]	yield[d] (%)	ee[e,f] (%)
1	**3a** (10)	12 h	10 min	A	94	96 (*S*)
2	**3a** (10)	12 h	5 min	A	92	96 (*S*)
3	**3a** (10)	12 h	2.5 min	A	86	95 (*S*)
4	**3a** (10)	12 h	2 min	A	81	96 (*S*)
5	**2** (20)	12h	5 min	A	84	87 (*S*)
6	**3a** (10)	20 min	5 min	B	98	81 (*S*)
7	**3a** (10)	10 min	5 min	B	97	98 (*S*)
8	**3a** (10)	5 min	5 min	B	95	97 (*S*)
9	**3a** (10)	2.5 min	5 min	B	90	93 (*S*)
10	**1** (20)	10 min	5 min	B	93	90 (*R*)
11	**2** (20)	10 min	5 min	B	87	70 (*S*)
12	**3b** (10)	10 min	5 min	B	93	72 (*S*)
13	**3c** (10)	10 min	5 min	B	97	5 (*S*)

[a] All reactions were run on a 0.25 mmol scale using chiral ligands. [b] Time 1: arylzinc formation. Time 2: catalyzed addition to aldehydes. [c] Method A: first at 60 °C for 12 h (time 1), then after addition of ligand and carbonyl compound with 300 W μw irradiation to 60 °C (time 2)). Method B: with 300 W μw irradiation to 60 °C (time 1), followed by addition of ligand and carbonyl compound under the same conditions (time 2). [d] Isolated yield of the corresponding product. [e] Enantiomeric excesses were determined by chiral HPLC (Chiralcel OD-H, see the Supporting Information for details). [f] Absolute configuration assigned by comparison with literature data.[2]

reactions can be influenced also by microwave irradiation.[6] In all these cases, it has been demonstrated that the use of μw irradiation can dramatically cut reaction times often accompanied with increased product purities and yields.[7]

In this report, we present our recent results in the catalytic arylation of aromatic aldehydes with aromatic boronic acids using conformationally restricted, aziridine-based amino alcohol ligands derived from amino acids. In addition, the impact using μw irradiation vs conventional heating is discussed. To the best of our knowledge, this is first report where microwave irradiation is used as a convenient energy source in the catalytic enantioselective arylzinc addition to aldehydes. In continuation of our studies concerning the utilization of easily obtainable amino alcohols as chiral, nonracemic ligands, we synthesized the aziridine-containing ligands **3a**−**c** to evaluate their potential as catalysts for the asymmetric arylzinc addition to aldehydes. The aziriridines were chosen because their rigidity and strong "curvature" in the substituent angles will provide less flexibility in the catalytically active complex. Thus, if these angles fit and the substituents are selected well, they should be better ligands than the more flexible counterparts **1** and **2**, respectively. If the fit is unsatisfactory, however, the results should also be more drastic in the negative sense, and may guide to a clear insight of the orientation of the ligands in the catalytically active species.

The rigid compounds **3a**−**c** were prepared in high yields and multigram quantities starting from L-serine and L-threonine following the procedure described by Zwanenburg et al.[8]

With this set of ligands, our attention was turned toward the evaluation of the reaction conditions. As illustrated in Table 1, the reaction time to achieve the formation of the zinc reagent starting from boronic acid and diethyl zinc is 12 h (time 1) at 60 °C. After addition of the carbonyl component, the reaction mixture is stirred for an additional 12 h (time 2) at different temperatures, upon which TLC monitoring revealed complete consumption of the starting materials (Table 1). The reaction times reported here are in agreement to the ones reported by others.[2,3,9]

Aziridines **3a** (R = H and R_1 = Ph) and **3b** (R = H and R_1 = Et) give comparable selectivities to those obtained with ligands **1** and **2** (Table 1, entries 1, 2 vs 3, 4). Further structural diversification of the aziridine ligands revealed that **3c** (from threonine) gives almost no stereoselectivity (entry 5). The 2,3-cis-disubstituted aziridine ring system obviously does not favor the formation of a productive transition state allowing stereodifferentiation.

Therefore, no further optimization was done on 2,3-disubstituted aziridines. In terms of efficiency, the amount of the ligand **3a** can be reduced to 10 mol % without any relevant change of the enantiomeric excess (Table 1, entry 6), while reduction to 5 mol % results in a slight decrease (entry 7). Lowering the reaction temperature from rt to 0 °C was found to have only a small influence on the enantioselectivity (entry 8). However, the selectivity decreased to 80% ee using higher reaction temperatures (60 °C, entry 9), although the yield remained almost quantitative.

After improved conditions for the conventional reaction were defined, our efforts were focused on the influence of microwave irradiation (Table 2).

There is experimental evidence that certain chemical transformations lead to different results in terms of speed and enantioselectivity by using either microwave or conventional heating in a flask at the same measured reaction temperature.[10]

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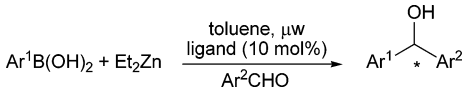
TABLE 3. Microwave-Assisted Aryl Transfer to Aldehydes Using Ligand 3a[a]



entry	Ar^1	Ar^2	yield[b] (%)	ee[c,d] (%)
1	Ph	*p*-MePh	97	98 (*S*)
2	Ph	*o*-MePh	98	93 (*S*)
3	Ph	*p*-ClPh	93	93 (*S*)
4	Ph	*o*-ClPh	88	98 (*S*)
5	*p*-ClPh	Ph	90	89 (*R*)
6	*p*-MePh	Ph	96	70 (*R*)

[a] Reactions were performed on a 0.25 mmol scale with $PhB(OH)_2$ (2.4 equiv) and Et_2Zn (7.2 equiv) in toluene with 300 W μw irradiation of to 60 °C for 10 min, subsequent addition of ligand and carbonyl compound under the same conditions for 5 min. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC (Chiralcel OD-H). [d] Absolute configuration assigned by comparison with literature data.[2]

The postive thermal effects of microwave heating can be explained by the different heating kinetics similar to a microreactor thermal exchange and possibly a different reaction vessel wall involvement rather than by a doubtful special microwave effect.[6]

Reactions were performed with a single-mode cavity in sealed, heavy-walled Pyrex tubes. In preliminary experiments, the reaction time required for the arylzinc additon to the aldehyde (time 2) was varied using 10 mol % of the catalyst **3a**, microwave irradiation at 300 W, and temperatures up to 60 °C (method A). A reaction time of 10 min furnished the desired product in high yield and high enantioselectivity (Table 2, entry 1). Reduction of the reaction time from 10 to 5 min did not alter the degree of enantioselectivity of the reaction (entry 2). Further shortening the reaction time (time 2) to 2.5 or 2 min resulted in incomplete conversion, while the enantiomeric excess of the product remained unaffected (entries 3 and 4). By using ligand **2**, the chiral diarylmethanol was obtained in lower yield and enantioselectivity (entry 5).

More interestingly, though, is the fact that the reactive arylzinc species also can be effectively generated under microwave irradiation. Consequently, the desired diarylmethanols can be obtainded in high yields and ee's (method B). Thus, the best reaction conditions established for this particular reaction consist of 10 min (Table 2, time 1) for the generation of the arylzinc species, followed by the addition of the catalyst and the appropriate aldehyde and an additional irradiation time of only 5 min (Table 2, time 2). This afforded the chiral diarylmethanol in 98% ee (entry 7). This is a significant improvement over previously reported protocols. Increasing the arylzinc formation time (time 1) to 20 min or decreasing it to 5 or 2.5 min led to a slight reduction of both ee and yield (Table 2, entries 6, 8, and 9). We hypothesized that $ZnPh_2$ can be formed under microwave irradiation by using 20 min as a reaction time (time 1), and this species likely promotes the addition faster than the amino alcohol based catalyst promotes the asymmetric addition. A similar proposal was advanced by Bolm[11] in reactions that began with $ZnPh_2$.

While utilizing ligands **1** and **2**, the resulting diarylmethanols were obtained in lower yields and ee's compared to ligand **3a** (entries 10, 11 vs entry 7). Aziridine ligand **3a** also led to high levels of enantiocontrol. In comparison, catalysts **3b** and **3c** (entries 12, 13) promote the reaction less efficiently and with lower enantioselectivity than ligands **1** and **2**. Under the optimized microwave conditions no ethyl transfer was detected; since phenyl transfer is some orders of magnitude faster, as observed previously by others[12,13] for the addition of Ph_2Zn/Et_2Zn in a conventional experiment.

With reaction time, yield, ee, and catalyst optimized, the scope of the reaction system with various aromatic boronic acids and aldehydes of diverse electronic and steric properties was examined.

Phenylboronate underwent smooth aryl addition to *o*- and *p*-tolaldehyde in almost quantitative yields and with very high ee (Table 3, entries 1 and 2).

Changing to electron-withdrawing substituents in the carbonyl compound did not result in a different behavior; the enantioselectivities remained high (Table 3, entries 3 and 4). In order to examine some substituent effects of the aryl groups to be transferred, substituted aryl boronic acids were studied. Also with these, high yields and good enantiomeric excesses were obtained (entries 5, 6). For example, aryl transfer reaction from *p*-chlorophenyl boronic acid to benzaldehyde occurred with 89% ee (Table 3, entry 5); however, the tolyl derivative reacted less selectively (entry 6)

In summary, we have demonstrated an efficient and very fast catalytic enantioselective arylation of aromatic aldehydes under microwave "flash-heating" using rigid chiral ligands readily available from common amino acids. The major advantage of microwave irradiation is the considerable reduction in reaction time without loss of enantioselectivity.

Experimental Section

General Procedure for the Asymmetric Arylation of Aldehydes. (1) Typical Experimental Procedure for Reactions Performed without Microwave Irradiation (Table 1, Entry 6). Diethylzinc (3.6 mL, 3.6 mmol, toluene solution) was added dropwise to a solution of phenylboronic acid (146.2 mg, 1.2 mmol) in toluene (2 mL) under an argon atmosphere. After being stirred for 12 h (time 1) at 60 °C, the mixture was cooled to room temperature and a solution of the chiral amino alcohol **3a** (23.4 mg, 0.05 mmol, 10 mol %) in 1 mL of toluene was added. The reaction was stirred for 15 min, and a solution of *p*-tolualdehyde (60 mg, 0.5 mmol) in toluene was subsequently added. After being stirred overnight (time 2) the reaction was quenched with water and the aqueous layer was extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and filtered, and the solvents were evaporated under reduced pressure. Purification by flash chromatography on silica, eluting with a mixture of hexane/ethyl acetate (90:10), gave 96.1 mg (0.49 mmol, 97% yield, 96% ee) of (*S*)-(4-methyphenyl)phenylmethanol as a white solid. NMR ^1H ($CDCl_3$, 400 MHz): δ = 7.31−7.08 (m, 9H), 5.68 (s, 1H), 2.55 (s, 1H), 2,29 (s, 3H). NMR ^{13}C ($CDCl_3$, 100 MHz): δ = 143.9, 140.9, 137.1, 129.0, 128.3, 127.3, 126.4, 126.4, 75.9, 21.0. HRMS calcd for $C_{14}H_{14}O$ $(M)^+$: 198.1045, found 198.1046. HPLC separation conditions: Chiralcel OD, hexane/i-PrOH 90:10, 0,5 mL/min, λ = 254 nm, $t_R(R)$: 19.1 min, $t_R(S)$: 21.1 min.

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(2) For Reactions Performed under Microwave Irradiation. Typical Experimental Procedure: Method A (Table 2, Entry 2). Diethylzinc (1.8 mL, 1.8 mmol, toluene solution) was dropwise added to a solution of phenylboronic acid (73.1 mg, 0.6 mmol) in toluene (1 mL) under argon atmosphere in a sealed vessel. After being stirred for 12 h (time 1) at 60 °C, the mixture was cooled to room temperature and a toluene solution of the chiral amino alcohol **3a** (11.7 mg, 0.025 mmol, 10 mol %) in 1 mL of toluene was added. The reaction was stirred for an additional 15 min, and the *p*-tolualdehyde (30 mg, 0.25 mmol) solution was added subsequently. The reaction vessel was irradiated at 300 W in a specialized microwave reactor oven and heated to 60 °C for 5 min (Time 2). After cooling, the reaction mixture was quenched with water and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and filtered and the solvents evaporated under reduced pressure. Purification by flash chromatography on silica eluting with a mixture of hexane/ethyl acetate (90:10) gave 45.6 mg (0.23 mmol, 92% yield, 96% ee) of the pure (*S*)-(4-methyphenyl)phenylmethanol as a white solid. NMR ^{1}H ($CDCl_3$, 400 MHz): $\delta = 7.31-7.08$ (m, 9H), 5.68 (s, 1H), 2.55 (s, 1H), 2,29 (s, 3H). NMR ^{13}C ($CDCl_3$, 100 MHz): $\delta = 143.9$, 140.9, 137.1, 129.0, 128.3, 127.3, 126.4, 126.4, 75.9, 21.0. HRMS calcd for $C_{14}H_{14}O$ $(M)^+$: 198.1045, found 198.1046. HPLC separation conditions: Chiralcel OD-H, hexane/i-PrOH 90:10, 0,5 mL/min, $\lambda = 254$ nm, $t_R(R)$: 17.6 min, $t_R(S)$: 19.9 min.

Typical Experimental Procedure: Method B. Diethylzinc (1.8 mL, 1.8 mmol, toluene solution) was added dropwise to a solution of boronic acid (0.6 mmol) in toluene (1 mL) under an argon atmosphere in a sealed vessel. The mixture was irradiated for 10 min (time 1) at 60 °C, with an irradiation power of 300 W in a specialized microwave reactor oven. A toluene solution of the chiral amino alcohol **3a** (11.7 mg, 0.025 mmol, 10 mol %) in 1 mL of toluene was added. The reaction was stirred for 15 min and the aldehyde (0.25 mmol) solution added subsequently. The reaction vessel was irradiated again at 300 W to 60 °C for 5 min (time 2). After cooling, the reaction mixture was quenched with water and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and filtered and the solvents evaporated under reduced pressure. Purification by flash chromatography on silica eluting with a mixture of hexanes/ethyl acetate (90:10) afforded the pure diarylmethanols.

(*S*)-(2-Chlorophenyl)phenylmethanol (Table 3, Entry 4). Reagents: Diethylzinc (1.8 mL, 1.8 mmol, toluene solution), phenylboronic acid (73.1 mg, 0.6 mmol), chiral amino alcohol **3a** (11.7 mg, 0.025 mmol, 10 mol %), and 2-chlorobenzaldehyde (35.2 mg, 0.25 mmol). The crude product was then purified on silica gel eluting with a mixture of hexane/ethyl acetate (90:10) to give 48 mg (0.22 mmol, 88% yield, 98% ee) of the pure (*S*)-(2-chlorophenyl)phenylmethanol as a white solid. NMR ^{1}H ($CDCl_3$, 400 MHz): $\delta = 7.58-7.18$ (m, 9H), 6.18 (s, 1H), 2.48 (s, 1H). NMR ^{13}C ($CDCl_3$, 100 MHz): $\delta = 142.2$, 140,9, 129.50, 128.70, 128.57, 128.4, 128.1, 128.0, 127.8, 127.7, 127.0, 126.8, 72.6. HRMS calcd for $C_{13}H_{11}OCl$ $(M)^+$: 218.0498, found 218.0497 Chiralcel OD, hexane/*i*-PrOH 90:10, 0.5 mL/min, $\lambda = 254$ nm, $t_R(R)$: 15.9 min, $t_R(S)$: 19.8 min.

(*R*)-(4-Chlorophenyl)phenylmethanol (Table 3, Entry 5). Reagents: Diethylzinc (1.8 mL, 1.8 mmol, toluene solution), 4-chlorophenylboronic acid (93.9 mg, 0.6 mmol), chiral amino alcohol **3a** (11.7 mg, 0.025 mmol, 10 mol %), and benzaldehyde (26.5 mg, 0.25 mmol). The crude product was then purified on silica gel eluting with a mixture of hexane/ethyl acetate (90:10) gave 49 mg (0.22 mmol, 90% yield, 89% ee) of the pure (*R*)-(4-chlorophenyl)phenylmethanol as a white solid. NMR ^{1}H ($CDCl_3$, 400 MHz): $\delta = 7.32-7.22$ (m, 9H), 5.74 (s, 1H), 2.39 (s, 1H). NRM ^{13}C ($CDCl_3$, 100 MHz): $\delta = 143.4$, 142.2, 133.2, 128.5, 128.5, 127.8, 127.8, 126.5, 75.56. HRMS calcd for $C_{13}H_{11}OCl$ $(M)^+$: 218.0498, found 218.0499 Chiralpak AD-H, hexane/*i*-PrOH 90:10, 1 mL/min, $\lambda = 254$ nm, $t_R(R)$: 13.7 min, $t_R(S)$: 15.2 min.

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Supporting Information Available: General experimental methods and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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