Ultrasound-Assisted, Transition-Metal-Free Synthesis of Diaryl Tellurides from Aryl Boronic Acids: A Possible Free-Radical Mechanism

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Abstract: The first rapid, catalyst-free synthesis of diphenyl tellurides from readily available diphenyl ditelluride and aryl boronic acids is reported. The high efficiency, general applicability and wide substrate scope, including heterocycles and other functional groups, make this method superior. The technique, which utilizes dimethyl sulfoxide solvent and ultrasound promotion, opens the door for the synthesis of diphenyl tellurides at 100 °C in air within a short time in high yields.

Key words: arylation, cross-coupling, free radicals, diphenyl telluride, transition metals

During the past decade, organotellurium chemistry has attracted considerable, ongoing attention due to its importance in different areas of chemistry. In organic synthesis, organotellurium compounds are well known as intermediates[1a] in group transfer cyclization reactions. For example, as group transfer agents, secondary alkyl phenylorganotellurium compounds have been shown to be effective radical precursors in terms of chemoselectivity and yield in dialkylzinc-mediated radical addition reactions.[1b] Numerous applications of organotellurium compounds as novel initiators for controlled/living radical polymerization[2a,b] have been described. Organotellurium-based ligands have been reported as efficient metal complexation reagents in inorganic chemistry due to their 'soft' donor nature, and they can function as either Lewis acids or Lewis bases.[2c] The use of organochalcogen compounds in asymmetric synthesis is also a most curious development that has led to a new direction in the area of organometallic chemistry.[3]

Organotellurium compounds also exhibit diverse biological activities and, indeed, anticancer activity of such compounds have been shown.[4a] Much attention has therefore been paid to the synthesis of organotellurium compounds that can be used as enzyme mimics and chemotherapeutic agents and, particularly, water-soluble organotellurium compounds **1**–**3** (Figure 1), which have been shown to be potent thiol peroxidase and antioxidants.[4b] Tellurium-based drugs such as ammonium trichloro(dioxoethylene-*O*,*O*′)tellurate and 4,4′-dihydroxydiphenyltelluride are used as enzyme inhibitors for cysteine proteases and as redox modulators for glutathione,[4c] respectively. To synthesize the aforementioned tellurium compounds, various protocols have been reported. A general method involves the cross-coupling of diphenyl ditelluride with phenyl boronic acids or halobenzenes.

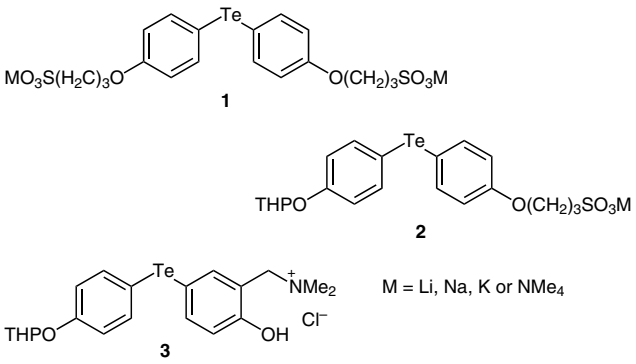

Figure 1 Some biologically active organotellurium compounds

Due to the difficulty in activating carbon–halogen bonds, cross-couplings between halobenzenes and diaryl dichalcogens usually require copper salts,[5] ligands,[5] reducing agents,[5b] and strong bases. In contrast, phenyl boronic acids are commercially available, are easily activated, and are also able to couple with diaryl dichalcogens. Wang et al.[6a] reported an iron-catalyzed, ligand-free coupling of diphenyl dichalcogens with aryl boronic acids in DMSO after 20 hours at high temperature (130 °C). Recently, Ranu and co-workers[6b] utilized $CuFe_2O_4$ nanoparticles in combination with DMSO (1.5 equiv) in polyethylene glycol (PEG) to catalyze similar couplings after 12 hours at 100 °C. Taniguchi[6c] reported the copper iodide/bipyridyl-catalyzed coupling of diphenyl dichalcogens with aryl boronic acids in a DMSO/water mixture in 12 hours at 100 °C. Alves and co-workers[6d] utilized glycerol as solvent, copper iodide as catalyst, and DMSO as an additive to promote the coupling of diphenyl dichalcogens with aryl boronic acids at 110 °C for 30 hours. The Wang group[6e] introduced $InBr_3$ as a new catalytic system for the coupling of diphenyl dichalcogens with aryl boronic acids at elevated temperature. All these methods used DMSO as the solvent and a copper source as the catalyst, and required long reaction times.

Most of the foregoing catalytic systems require a catalyst and long reaction time of at least 12 hours. Surprisingly, we found that a test reaction between diphenyl ditelluride and an aryl boronic acid in DMSO proceeded smoothly, affording the corresponding diphenyl telluride-coupled product in high yield in the absence of the usual necessary

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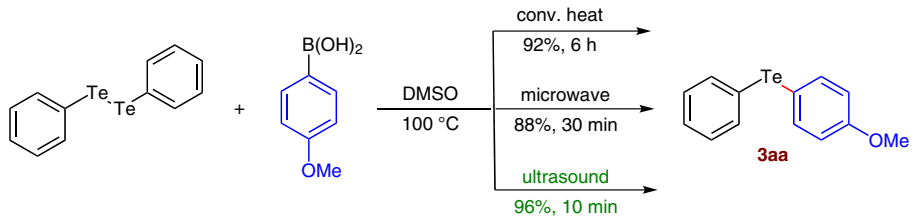


Scheme 1 Model reaction under three different conditions

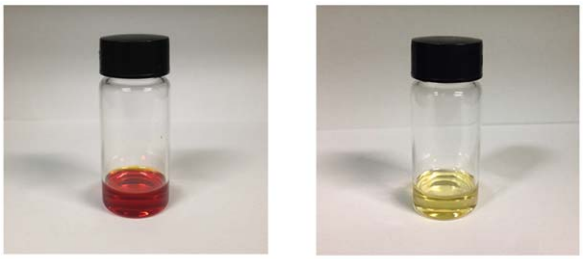
additives. Interestingly, the related reaction using diphenyl diselenide was ineffectual. Given the time required for the test reaction, we were prompted to utilize the findings from our previous reports on ultrasound irradiation[7] and organochalcogen chemistry[8] to examine activation by physical effects to obtain higher yields of diphenyl tellurides in shorter times. Thus, we surveyed the reactions of diphenyl ditelluride and 4-methoxyphenylboronic acid promoted by conventional heating, microwave, and ultrasound. All the reactions were performed at the same temperature (100 °C) and open to the air (Scheme 1). The ultrasound-assisted coupling afforded good yields within 10 min, compared with conventional heating (6 hours), and microwave (30 min). A slight decrease in temperature to 80 °C for 30 min resulted in lower yield (Table 1, entry 2).

To optimize the experimental conditions, we screened a wide range of solvents at 100 °C (Table 1). The reaction between diphenyl ditelluride and 4-methoxyphenylboronic acid in DMSO (3 mL) proceeded smoothly in air with ultrasound assistance.[9] The expected cross-coupled product, bis(4-methoxyphenyl)telluride, was obtained in 96% yield, again without the use of any additives. Other solvents such as *N*,*N*′-dimethylpropyleneurea (DMPU), dimethylformamide (DMF), *N*-methylpyrrolidone (NMP) and dimethylacetamide (DMAC) resulted in lower yields (entries 3–6). Unfortunately, none of the desired product was detected when the reaction was carried out in the green solvents glycerol or PEG 200 (entries 7 and 8). The reaction was sluggish in ethylene glycol (EG; entry 9). Product formation was easily identified by a change in the reaction color from an initial dark-orange to light-yellow at completion (Figure 2).

Table 1 Optimization of Reaction Conditions

Entry	Solvent	Temp. (°C)	Time (min)	Yield (%)[a]
1	DMSO	100	10	96
2	DMSO	80	30	65
3	DMPU	100	10	48
4	DMF	100	10	81
5	NMP	100	10	25
6	DMAc	100	10	49
7	PEG 200	100	10	ND
8	glycerol	100	10	ND
9	ethylene glycol	100	10	8
10	DMSO	100	30	88[b]
11	DMSO	100	360	92[c]
12	DMSO	100	30	<1[d]

[a] Determined by GC-MS analysis (with reference to diphenyl diselenide).
[b] Reaction with microwave (300 W).
[c] Reaction under conventional heating.
[d] Reaction under N_2 atmosphere.

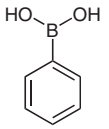
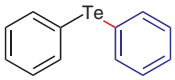
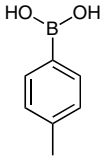
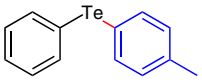
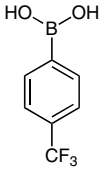
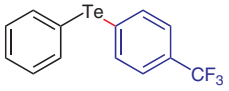
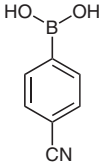
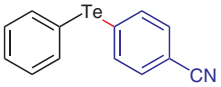
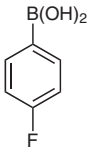
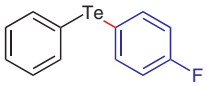
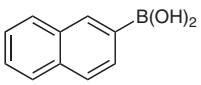
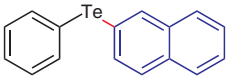
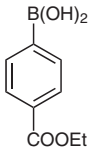
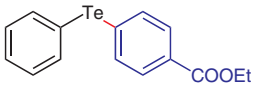
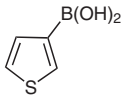
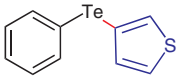
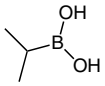
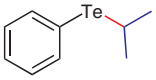
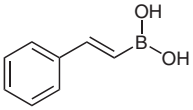
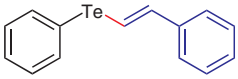


A **B**

Figure 2 Progress of the reaction: (A) Reaction at the beginning, and (B) at the end (10 min)

The optimized conditions were applied to various substituted aryl boronic acids to probe the substrate scope and reactivity. For all the cases in Table 2, the corresponding ultrasound-promoted cross-coupled products were obtained in good to moderate yields without employing any further additives. The coupling reactions between unsubstituted phenyl and naphthyl boronic acids with diphenyl ditelluride gave nearly quantitative yields (entries 1 and 6). Interestingly, the yield when using 4-methylphenyl boronic acid (entry 2) decreased somewhat, but was still good compared with 4-methoxyphenyl boronic acid, which afforded excellent yields. Substrates with electron-withdrawing groups on the aryl boronic acid, such as *p*-trifluoromethyl, *p*-cyano, *p*-fluoro, or *p*-ethoxycarbonyl, furnished coupled products in moderate yields along with

Table 2 Ultrasound-Promoted Cross-Coupling of Diphenyl Ditellurides and Substituted Phenyl Boronic Acids

Entry	Boronic acid	Product	Time (min)	Yield (%)[a]
1			10	99
2			15	87
3			15	72
4			15	72
5			15	70
6			15	91
7			5	64
8			10	90
9			20	NR
10			20	NR

[a] Determined by GC-MS analysis, based on average of two independent runs.

diphenyl telluride as a side product, which was confirmed by GC-MS analysis. Furthermore, the reaction with five-membered heterocycle 3-thiophene boronic acid provided the corresponding coupled product in high yields (entry 8). However, the fact that reactions with isopropyl and vinyl boronic acids did not proceed well under the present conditions (entries 9 and 10), indicates that the aromatic ring plays an important electronic role in the reaction. We also note that only a trace amount of product was detected when the experiments were conducted with phenyl boronic acids containing electron-withdrawing substituents (Table 2) under conventional heating even after prolonged reaction time. This result shows the significant importance of ultrasound irradiation technology in organochalcogen chemistry, particularly to synthesize unsymmetrical aryl tellurides. It is noted that, to our knowledge, this is the first report describing the coupling of diphenyl ditelluride with aryl boronic acids without metal sources, ligands, bases, or reducing agents with straightforward ultrasound assistance.

Regarding the mechanism of this reaction, experiments were conducted in the presence of radical scavengers hydroquinone and thiourea (2 equiv with respect to diphenyl ditelluride). Under these conditions, formation of desired product was observed in 8 and 7% yields, respectively, whereas 42% of the cross-coupled product was identified with the scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (Scheme 2). An increase in yield with TEMPO might be due to its instability in an air atmosphere. We therefore propose that the reaction proceeds through a free-radical pathway (Scheme 3). Furthermore, conducting the reaction under a N_2 atmosphere provided less than 1% cross-coupled product (Table 1, entry 12), which indicates that air is mandatory and plays an important role, presumably as oxidant.

In conclusion, we successfully achieved the cross-coupling of diphenyl ditelluride and aryl boronic acids in the absence of additives, and with the assistance of solvent, temperature, and ultrasonication.[11] The commercial availability of the reagents, exceptional functional group tolerance, and good to moderate yields make this an interesting alternative for the synthesis of unsymmetrical diaryl tellurides.

Acknowledgment

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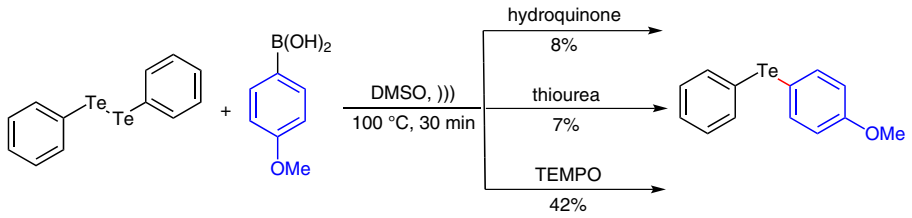
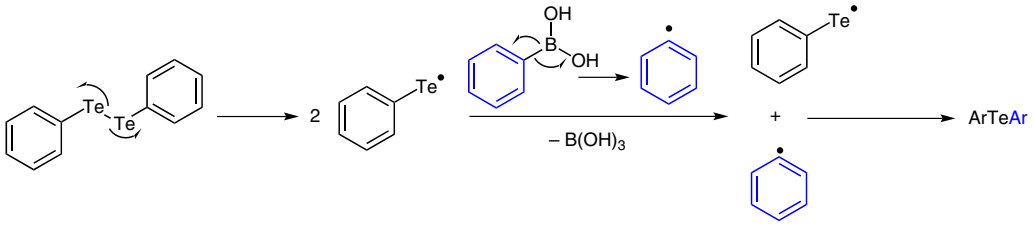


Scheme 2 Mechanistic investigations in the presence of radical scavengers



Scheme 3 Proposed free-radical mechanism for the synthesis of unsymmetrical aryl tellurides

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(11) **General Description:** Reagents were purchased from Aldrich Chemical Co., TCI and Strem Chemical Co. and were used as received. Reaction products were analyzed by GC-MS (Shimadzu-QP2010 SE), ^{1}H NMR and ^{13}C NMR (Varian Mercury Plus, 300 MHz). Chemical shift values are recorded as parts per million relative to tetramethylsilane as internal standard, unless otherwise indicated, and coupling constants are given in Hertz. A Fisher Scientific Sonic Dismembrator (model 500, 230 V, 50/60 Hz) was used for ultrasonication.

Cross-Coupling Reaction; General Procedure: Diphenyl ditelluride (0.12 mmol, 50 mg) and phenylboronic acid (0.27 mmol, 32 mg) were dissolved in DMSO (3 mL) followed by ultrasonication at 100 °C until color change from dark-orange to light-yellow (sometimes colorless) was observed. After usual work up, the crude product was analyzed by GC-MS and then purified by silica gel column chromatography. The purified products were characterized by ^{1}H and ^{13}C NMR spectroscopy. All synthesized compounds are known and their spectroscopic data were consistent with reported values.

4-Methoxyphenyl Phenyl Telluride: [6a] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 9 Hz, 2 H), 7.59–7.56 (m, 2 H), 7.21–7.17 (m, 3 H), 6.82 (d, *J* = 8.7 Hz, 2 H), 3.80 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0, 141.3, 136.6, 129.5, 127.4, 115.8, 115.7, 103.2, 55.3.

Diphenyl Telluride: [10] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 6.6 Hz, 4 H), 7.35–7.19 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 129.7, 128.1, 114.

4-Tolyl Phenyl Telluride: [6b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.8 Hz, 3 H), 7.29–7.17 (m, 4 H), 7.07 (d, *J* = 7.5 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9, 137.5, 137.4, 130.6, 129.7, 127.7, 115.4, 110.5, 21.5.

4-Trifluoromethyl Phenyl Phenyl Telluride: [5d] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (m, 2 H), 7.68 (m, 2 H), 7.42 (m, 3 H), 7.28 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.6, 138.2, 136.6, 130.0, 129.7, 128.9, 126.1 (q), 122.3,113.5.

4-Cyanophenyl Phenyl Telluride: [5d] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.82 (m, 2 H), 7.56 (d, *J* = 8.4 Hz, 2 H),

7.42–7.29 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 135.9, 132.4, 130.0, 129.4, 124.5, 118.9, 113.0, 110.8.

4-Fluorophenyl Phenyl Telluride: [6b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.63 (m, 4 H), 7.31–7.19 (m, 3 H), 6.99–6.90 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 161.6, 140.7, 138.2, 132.1, 129.8, 129.7, 128.0, 117.0, 114.8.

2-Naphthyl Phenyl Telluride: [6b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 6.3 Hz, 1 H), 7.82–7.66 (m, 7 H), 7.49–7.45 (m, 2 H), 7.32–7.19 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.1, 138.0, 137.9, 134.9, 134.5, 132.8, 129.7, 128.8, 128.0, 127.9, 127.6, 126.6, 126.5, 115.0, 112.2.

4-Ethoxycarbonylphenyl Phenyl Telluride: [6b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (m, 3 H), 7.62 (d, *J* = 8.1 Hz, 2 H), 7.40–7.25 (m, 4 H), 4.33 (q, *J* = 6.9, 7.2 Hz, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 139.5, 136.2, 130.2, 130.0, 129.7, 128.8, 123.1, 113.7, 61.1, 14.5.

3-Thiophenyl Phenyl Telluride: [6b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 1 H), 7.61–7.57 (m, 3 H), 7.31–7.16 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 137.0, 136.9, 136.7, 134.7, 129.7, 129.6, 128.0, 127.7, 127.4, 115.4, 104.0.

