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Iron-Catalyzed Radical Oxidative Coupling Reaction of Aryl Olefins with 1,3-Dithiane

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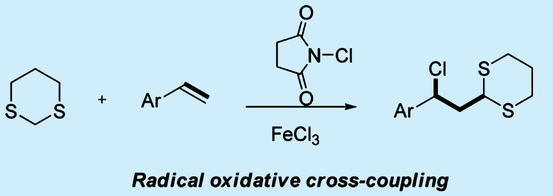
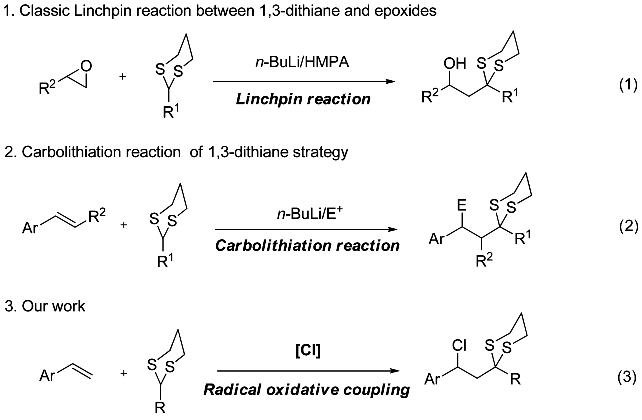
Supporting Information

ABSTRACT: An alternative method to an iron-catalyzed radical oxidative cross-coupling reaction followed by 2-chloro-1,3-dithiane and aryl olefins for the synthesis of β-chloro substituent 1,3-dithiane products is presented. The described method has the advantage of mildness of the reaction conditions and tolerates a variety of functional groups. Preliminary mechanistic studies have confirmed the first example of a coupling of 1,3-dithiane with unactivated alkenes that proceeds via an iron-catalyzed oxidative radical intermediate along the reaction pathway.



1, 3-Dithianes are widely used as attractive acyl anion equivalents (umpolung) for construction of carbon−carbon bonds for over half a century.[1] They have also been applied as building blocks for the preparation of a wide variety of chemicals and target molecules. For example, 1,3-dithiane anions can be frequently exploited for the generation of a wide variety of aldol linkages (linchpin reaction) and for the union of advanced fragments in numerous natural products synthesis[2] (Scheme 1, eq 1). We identified a modular set of 1,3-dithianes as being highly desirable for the installation of acyl relevant moieties. During the past few years, we disclosed a new carbolithiation protocol for the conversion of carbon−carbon bonds to 1,3-dithiane derivatives using lithiated 1,3-dithiane anions as electrophiles with olefinic substrates[3] (Scheme 1, eq 2). These alternative routes were important advances in this field and provided 1,3-dithiane protocols complementary to known chemistry. Despite significant improvements, the substrate scope of these reactions is limited, and these available methods suffer from issues of imperfect functional group tolerance. Further, the application of these reactions is particularly problematic for the polymerization process,[4] owing to our continuing studies in enantioselective carbolithiation transformations of styrenes with 1,3-dithiane.[5] Thus, it was necessary to discover a new strategy for direct functionalization of aryl olefins with 1,3-dithiane.

Scheme 1. Reactions of 1,3-Dithianes for Construction of Carbon−Carbon Bonds



Radical oxidative coupling reactions have provided increasingly important innovations for the construction of carbon−carbon and carbon−heteroatom bonds over the past decades.[6] In particular, radical oxidative cross-coupling methods by inexpensive iron catalyst provide a useful approach to C−C bond construction.[7] In 2009, Tu and co-workers reported a novel iron-catalyzed radical coupling reaction of alcohols with alkenes.[8] Similarly, Lei and co-workers have described a radical oxidative coupling of phenols and olefins using less expensive iron catalysts.[9] However, seeking novel RH or RXH as nucleophiles and applying them in alkene difunctionalization still remains a challenge.[10] There are relatively few reports on the addition of 1,3-dithiane to unactivated olefins,[11] possibly because the radical derived from 1,3-dithiane is relatively electron-rich, and the coupling reaction of 1,3-dithiane with alkenes was successful only when electron-deficient alkenes were employed.[11b] Herein, we present a method, based on the iron-catalyzed radical oxidative cross-coupling pathway manifolds, that concatenates simple 1,3-dithiane with available arylalkenes to form a wide range of dithiane derivatives (Scheme 1, eq 3). In addition, this protocol circumvents issues of alkene difunctionalization and proceeds efficiently under friendly iron-catalyzed conditions, allowing for excellent functional group compatibility.

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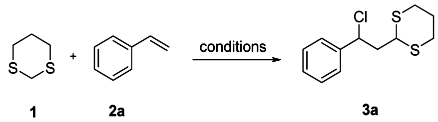
We started our initial investigations with the transformation of **1** into 1,3-dithiane derivative **3a** using various radical initiator sources and catalysts. We hypothesized that a readily accessible iron catalyst would be useful for this transformation, which it has shown to be effective in radical cross-coupling reaction of alkene. As shown in Table 1, $FeCl_3$ was utilized as the catalyst in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoqinone (DDQ) and gave little to no desired product in these reactions. Since 2-H-1,3-dithiane is sparingly stable in an $FeCl_3$ catalyst system, after some experimentation, we reasoned that use of an initiator might be beneficial and *N*-chlorosuccinimide (NCS) was necessary to facilitate the coupling in a preactivation step.[12] To our delight, upon warming to 0 °C, the aggregates 2-chloro-1,3-dithianes appear to disappear and 1,3-dithiane is efficiently converted with **2a** to furnish the desired product **3a** in 75% yield (Table 1). In contrast, none of the desired product was generated in these reactions when *N*-bromosuccinimide (NBS) was used. One possibility is that 2-bromodithiane in solution is unstable and unreactive. To test this postulate, we ran the reaction with NBS with 1,3-dithaine in 1,2-dichloroethane (DCE) without olefins and obtained oxidative hydrolysis results. We have now found that the amount of NCS is essential to the outcome of the reaction, which we propose occurs by electrophilic activation using $FeCl_3$ as a catalyst without the need for an added ligand, whereas the use of $FeCl_3$ (5−15 mol %) did not have a positive influence on the outcome of the reaction. The reaction performed best with use of a halogenated solvent such as DCE, whereas C−C bond formations were less efficient in solvents such as toluene, *N,N*-dimethylformamide (DMF), and tetrahydrofuran (THF).

Table 1. Cross-Coupling Reaction between 1,3-Dithiane and Styrene under Varied Conditions[a]

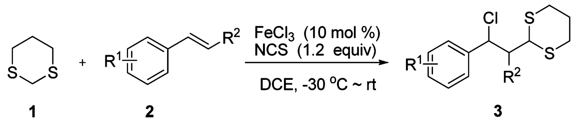


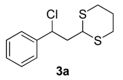
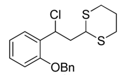
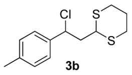
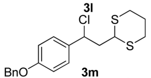
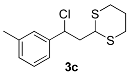
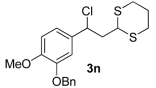
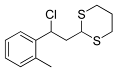
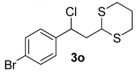
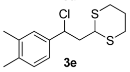
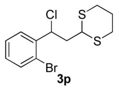
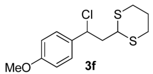
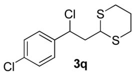
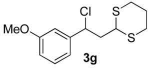
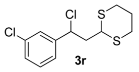
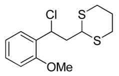
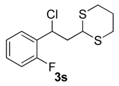
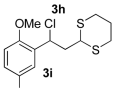
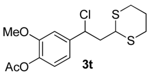
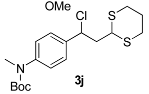
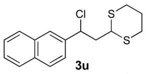
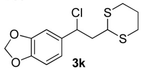
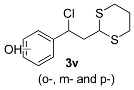
entry[b]	catalyst	activating agent	solvent	yield[c] (%)
1	$FeCl_3$ (10%)	DDQ	CH_2Cl_2	trace
2	CuI (15%)	DDQ	CH_2Cl_2	0
3	$PdCl_2$ (5%)	DDQ	CH_2Cl_2	trace
4	$FeCl_3$ (10%)	None	CH_2Cl_2	0
5	$FeCl_3$ (10%)	NCS	CH_2Cl_2	75
6	**$FeCl_3$ (10%)**	**NCS**	**DCE**	**86**
7	None	NCS	DCE	0
8	$FeCl_3$ (10%)	NCS	DCE	trace
9	$FeCl_3$ (5%)	NCS	DCE	83
10	$FeCl_3$ (15%)	NCS	DCE	84
11	$FeCl_3$ (10%)	NCS	toluene	0
12	$FeCl_3$ (10%)	NCS	DMF	0
13	$FeCl_3$ (10%)	NCS	THF	trace

[a]Reaction conditions: all of the reactions were performed with **1** (30 mg, 0.25 mmol), **2a** (23.4 mg, 0.225 mmol), catalyst, and activating agent (0.3 mmol) in 2 mL of solvent for 12 h. [b]The reaction temperature: rt to 100 °C (entries 1−4); 0 °C (entries 5−14). [c]Isolated yield.

With optimized reaction conditions in hand, the scope of these radical processes with regard to the arylalkenes and 1,3-dithiane was next examined (Table 2). We focused our attention on substitutions on the styrene ring. Electron-rich olefins gave good to excellent yields of cross-coupling products. By increasing the reaction temperature to rt, complete conversion of electron-deficient olefins to the desired products was achieved. In addition, aryl olefins with sterically hindered ortho substituents could also be obtained in moderate to good yields (Table 2, entries 4, 8, 12, 16, and 19). In these cases, the substrates shown gave clean conversion to the *β*-chloro substituted 1,3-dithiane derivatives. Substrates containing free OH substituents (*o*-, *m*-, and *p*-styrenes) have, to date, failed to be transformed to dithiane-coupling products (Table 2, entry 22). On a gram scale, the coupling of 1,3-dithiane with **2b** proceeded the desired product **3b** in 81% yield. Importantly, the dithiane moieties can be removed without loss of the Cl moiety, thereby providing a diverse series of correponding *β*-chloro substituted formyl systems. The above procedure proved to be general for the complementary to current protocols and allows for the synthesis of *β*-chloro substituted 1,3-dithiane derivatives that are not readily accessible via traditional linchpin and carbolithiation means.

Table 2. Iron-Catalyzed Cross-Coupling between 1,3-Dithiane and Alkenes[a]

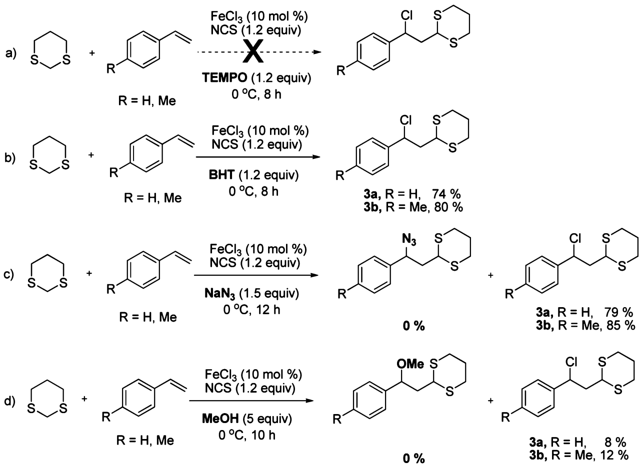


entry	product	t/°C	yield[b]	entry	product	t/°C	yield[b]
1	 **3a**	-10	86 %	12	 **3l**	rt	84 %
2	 **3b**	-30	89 %	13	 **3m**	rt	85 %
3	 **3c**	-30	91 %	14	 **3n**	rt	81 %[c]
4	 **3d**	-20	88 %	15	 **3o**	rt	80 %
5	 **3e**	-20	93 %	16	 **3p**	rt	74 %
6	 **3f**	0	85 %	17	 **3q**	rt	81 %
7	 **3g**	0	87 %	18	 **3r**	rt	77 %
8	 **3h**	10	82 %	19	 **3s**	rt	79 %
9	 **3i**	rt	83 %[c]	20	 **3t**	0	78 %
10	 **3j**	0	80 %[c]	21	 **3u**	-10	93 %
11	 **3k**	rt	82 %[c]	22	 **3v** (o-, m- and p-)	0	n.d.

[a]Reaction conditions: 1,3-dithiane **1** (0.25 mmol), alkene **2** (0.225 mmol), NCS (1.2 equiv), $FeCl_3$ (10 mol %), 2 mL of DCE, −30 °C to rt, 24 h. [b]Isolated yield. [c]Reaction time: 2 h.

In order to aid our interpretation of the mechanism, a series of experiments were performed as outlined in Scheme 2. Initially, we found that no desired product was formed in the

Scheme 2. Mechanistic Experiments



presence of an excess of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), strongly indicating that the coupling transformation might proceed via a radical pathway (Scheme 2, a). To our surprise, when 2,6-di-*tert*-butyl-4-methylphenol (BHT, 1.2 equiv) was added under the standard conditions, the coupling reaction still afforded desired product in good yields. These results might disfavor the 1,3-dithiane radical anion transfer to phenol radical (Scheme 2, b). To gain a more thorough understanding of the origin of radical pathway, we carried out several competition experiments. The Cl substituent product was obtained when the reaction was performed in the presence of a large quantity of NaN_3 under standard reaction conditions, suggesting that the coupling might not occur through attack by the nucleophilic N_3 anion[13] (Scheme 2, c). However, the yield of desired product **3** was dropped quickly by trapping with 5 equiv of methanol.[14] It is highly likely that methanolysis of the 1,3-dithiane substrate interfered with the success of the coupling reaction (Scheme 2, d).

Subsequently, electron paramagnetic resonance (EPR) experiments were performed under optimized conditions. All EPR signals were detected with a *g*-factor of 9.447. As shown in Figure 1A, no EPR signal was observed when the mixture of **1** and NCS was tested. The EPR experiment of the mixture of **1**, $FeCl_3$, and NCS displayed a strong signal peak (orange line), suggesting that $FeCl_3$ should be assigned to form 1,3-dithiane radical initially. According to Figure 1B, we monitored the cross-coupling reaction of **1** and **2a** by EPR spectroscopy. After $FeCl_3$ was added to the mixture of **1**, **2a**, and NCS, a strong signal peak was observed clearly (25 min); these EPR results indicated that catalyst $FeCl_3$ activated the above reaction system to give reactive radicals. After 50 min, the signal peaks slowly became weak. It demonstrated that the new generated radicals would be consumed by nucleophile **2a** during the coupling reaction process.

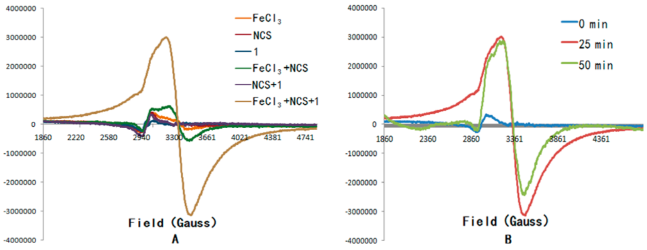
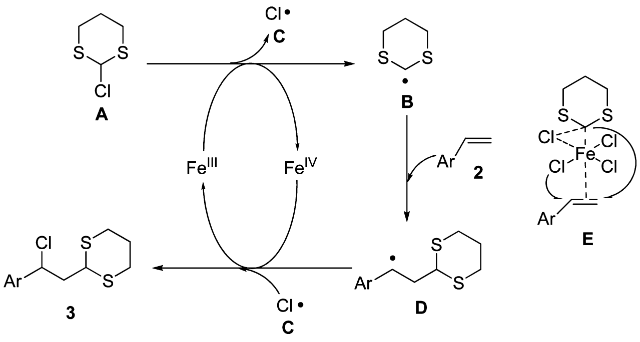


Figure 1. (A) EPR spectra from the reaction between (1) $FeCl_3$, **1**, NCS; (2) NCS and **1** or $FeCl_3$; (3) the mixture of $FeCl_3$, **1**, and NCS in DCE at room temperature. (B) EPR spectra acquired during the cross-coupling reaction time course between **1** and **2a**.

According to the above experimental results, a plausible explanation of mechanism is depicted in Scheme 3. After the generation of 2-chloro-1,3-dithiane **A**, $FeCl_3$ as a catalyst might afford radical 1,3-dithiane **B**[15] and [Cl] **C** species via a SET/radical pathway for C−Cl bond cleavage, which might promote the radicals and assist addition with alkenes **2** to produce the corresponding radical intermediate **D**. Subsequently, the generation of radical intermediate could be direct trapped by radical Cl to give the desired product **3**. The alternative explanation is that 2-chloro-1,3-dithiane can coordinate catalyst $FeCl_3$ to afford $[Fe]^{IV}$-intermediate **E** followed by simultaneous free-radical addition and a Cl transfer to give the coupling product. At present, there are still uncertainties concerning the mechanism that governs this transformation. However, we favor the explanation that proceeds via an iron-catalyzed radical oxidative coupling pathway.

Scheme 3. Proposed Mechanism



In conclusion, we have reported a new and efficient protocol involving the radical oxidative cross-coupling process, which holds great promise in the 1,3-dithiane area of diversity-oriented synthesis. In addition, the application of this new method to alkene derivatives led us to obtain 1,3-dithiane derivatives in high yields, making this method suitable for synthetic purposes in a one-pot procedure. Further investigations into the mechanism of this reaction as well as extensions of the substrate scope are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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