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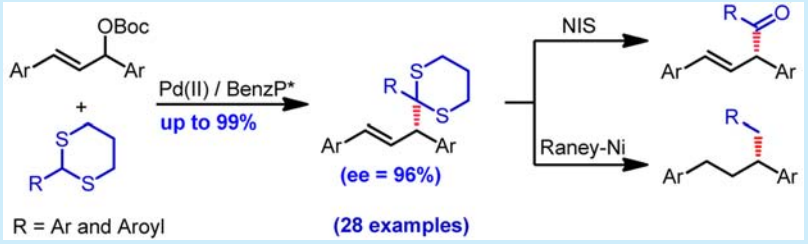
1,3-Dithianes as Acyl Anion Equivalents in Pd-Catalyzed Asymmetric Allylic Substitution

Kun Yao,[†] Delong Liu,*[,†] Qianjia Yuan,[‡] Tsuneo Imamoto,[‡,§] Yangang Liu,[†] and Wanbin Zhang*[,†,‡]

[†]School of Pharmacy and [‡]School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. China

Supporting Information



ABSTRACT: A Pd-catalyzed asymmetric allylic substitution with 1,3-dithianes as acyl anion equivalents has been developed in high yields and excellent enantioselectivities. The reaction was performed on a gram scale, and the corresponding alkylated products were conveniently converted into several biologically active products. This work provides an alternative strategy utilizing electrophilic carbonyl compounds as nucleophilic species in a Pd-catalyzed allylic substitution.

The 1,3-dithiane unit (Figure 1, **A**), a masked carbonyl group, is often used as an acyl anion synthon **I** due to its

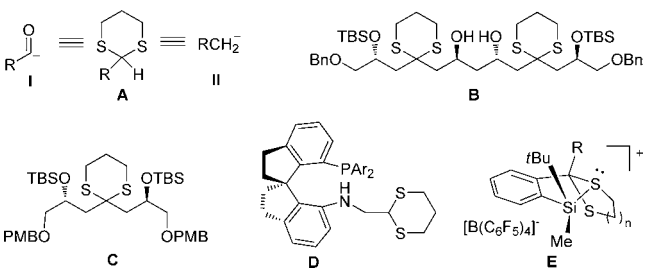
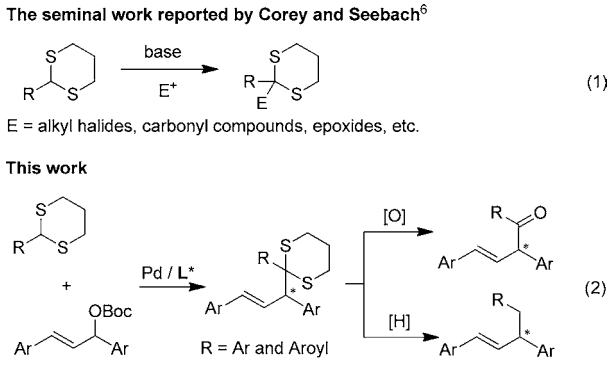


Figure 1. 1,3-Dithiane and its derivatives.

reversed-polarity or can alternatively act as a carbanion **II** via a final reductive desulfurization (sulfur−hydrogen exchange).[1] Therefore, 1,3-dithiane **A** is useful for the construction of many important organic compounds. Such examples include the key intermediates, **B** and **C**, for the synthesis of an antibiotic[2] and an antitumor compound,[3] respectively. Additionally, it is known that the introduction of a dithiane species can also significantly improve the catalytic efficiency of chiral ligands **D**[4] and catalysts **E**.[5]

Since the seminal work reported by Corey and Seebach (Scheme 1, eq 1),[6] numerous reactions of 1,3-dithianes have been reported. For example, 1,3-dithianes were allowed to react with many electrophiles, such as alkyl halides,[7a−e] carbonyl compounds,[7f,g] and epoxides.[7h−l] Despite these significant achievements, to the best of our knowledge, the use of 1,3-dithianes as acyl anion and carbanion equivalents in transition-metal catalyzed asymmetric reactions has not yet been reported.[8]

Scheme 1. 1,3-Dithianes as Acyl Anion Equivalents



Transition-metal-catalyzed allylic substitution is a powerful synthetic tool for the formation of C−C and C−X bonds (X = N, O, S, etc.).[9] Recently, we have developed several metal-catalyzed asymmetric allylic alkylations for the construction of biologically active chiral molecules with excellent catalytic behavior.[10] To further develop novel asymmetric allylic substitutions, we envisioned that 1,3-dithianes would be suitable nucleophiles as acyl anion equivalents for use in the above reaction. Recent studies have revealed several examples adopting different acyl anion equivalents in asymmetric allylic substitutions. Trost reported the use of the sodium salt of 1-phenylsulfonyl-1-nitroethane as an acetyl equivalent in a Pd-

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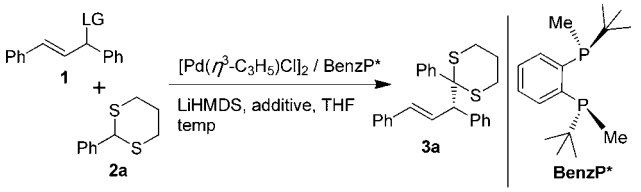
catalyzed asymmetric allylic substitution for the total synthesis of hygromycin A.[11] Evans developed a regio- and stereospecific Rh-catalyzed allylic substitution with trialkylsilyl-protected alkenyl cyanohydrins as acyl anion equivalents, which permits the construction of acyclic quaternary-substituted α,β-unsaturated ketones.[12] Carreira disclosed the use of formaldehyde *N,N*-dialkylhydrazones as neutral C1-nucleophiles in an Ir-catalyzed substitution of allylic carbonates.[13] To complement these interesting discoveries, we herein report a Pd-catalyzed asymmetric allylic substitution using 1,3-dithianes as acyl anion equivalents. To our delight, the reaction proceeded smoothly and the resulting chiral products could be conveniently transformed into several biologically active compounds via either oxidative or reductive desulfurization (Scheme 1, eq 2).

Our initial experiment was conducted with the reaction of 1,3-diphenylallyl pivalate (**1a**) and 2-phenyl-1,3-dithiane (**2a**). The reaction was carried out using a catalytic system consisting of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and a chiral ligand with LiHMDS as a base under a nitrogen atmosphere in THF at room temperature for 12 h. The effect of the ligand on the reaction was examined first, and chiral diphosphine ligands provided the most promising results.[14] BenzP* was found to be the best ligand with the desired product being obtained in 41% yield and with 78% ee (Table 1, entry 1). LiF, LiCl, LiBr, and LiI were then used as additives to improve the yield and enantioselectivity of the alkylated product (Table 1, entries 2–5).[15] The use of LiI gave **3a** in 92% ee but still with only a moderate isolated yield owing to the formation of a byproduct (Table 1, entry 5).[14] Therefore, we lowered the reaction temperature in order to suppress side reactions and improve product yield (Table 1, entries 6–8). To our delight, the desired product was obtained in up to 74% yield at 0 °C without any negative effect on the enantioselectivity (Table 1, entry 6). Further lowering of the reaction temperature to −20 °C led to an increase in enantioselectivity but a sharp decline in yield (Table 1, entry 7), and no reaction occurred at −40 °C (Table 1, entry 8). Finally, allylic substrates bearing OBoc (**1b**) and OAc (**1c**) leaving groups were examined at −20 °C (Table 1, entries 9 and 10). Compound **1b** bearing OBoc as a leaving group provided the best result (95% yield and 96% ee) (Table 1, entry 9). The effect of different bases, such as NaHMDS, KHMDS, and LDA, on the reaction was studied, and LiHMDS was found to be the most effective base.[14]

With the optimized reaction conditions in hand (Table 1, entry 9), nucleophiles **2** with different aryl substituents were explored (Scheme 2). 2-Aryl-1,3-dithianes bearing a Me group at the 3- or 4-position of the phenyl ring were examined first, with both reactions affording excellent enantioselectivities (**3b** and **3c**). 2-Aryl-1,3-dithianes with electron-withdrawing groups on the phenyl ring were next considered. Substrates bearing a F atom at the 2- or 4-position of the phenyl ring provided higher enantioselectivity than that of 2-(3-fluorophenyl)-1,3-dithiane (**3d** and **3f** vs **3e**). Compound **3f** was obtained in only moderate yield. We also carried out the reaction with a 2-aryl-1,3-dithiane bearing a Me group at the 2-position; however, no desired product was observed. Substrates **3g** and **3h** with Cl and Br atoms at the 4-position of the phenyl ring were then used, providing the corresponding products with excellent yields and good enantioselectivities. When the phenyl ring was replaced by a 2-naphthyl or thienyl group, the reaction proceeded smoothly with the desired products being obtained with excellent yields and enantioselectivities (**3i** and **3j**). Finally, an allyl substrate with Me at para-positions of the phenyl rings was used and the corresponding **3k** was obtained

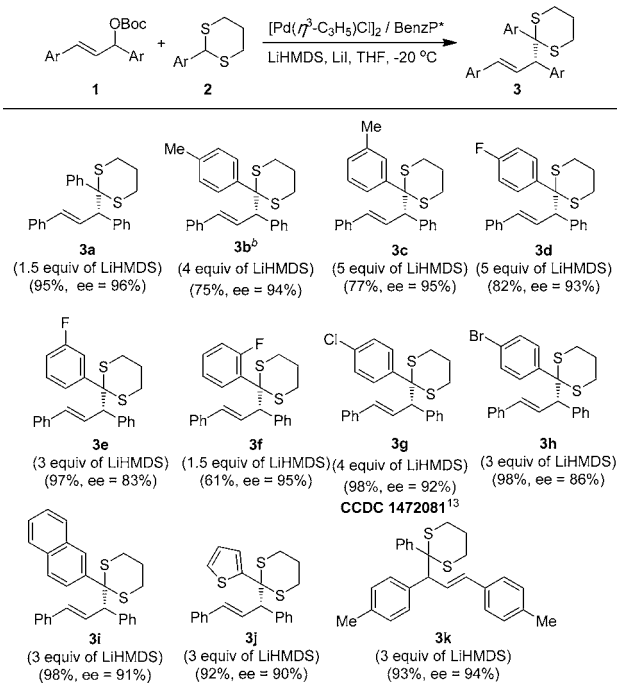
Table 1. Optimization of Reaction Conditions[a]



entry	additive	temp (°C)	LG	yield (%)[b]	ee (%)[c]
1	–	20	OPiv	41	78
2	LiF	20	OPiv	42	68
3	LiCl	20	OPiv	trace	72
4	LiBr	20	OPiv	34	90
5	LiI	20	OPiv	52	92
6	LiI	0	OPiv	74	92
7	LiI	−20	OPiv	30	95
8	LiI	−40	OPiv	N.R.	–
9	LiI	−20	OBoc	95	96
10	LiI	−20	OAc	51	80

[a]Unless otherwise noted, the reaction of **1** (0.1 mmol) with **2a** (0.2 mmol) was carried out using a catalytic system consisting of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) and BenzP* (5.5 mol %) under a N_2 atmosphere in the presence of LiHMDS (0.15 mmol) and an additive (0.1 mmol) in THF (3 mL) at the indicated temperature for 12 h. [b]Isolated yields. [c]Determined by HPLC using a chiral Daicel OD-H column.

Scheme 2. Scope of Substrates[a]



[a]Unless otherwise noted, the reaction of **1** (0.1 mmol) with **2** (0.2 mmol) was carried out using a catalytic system consisting of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) and BenzP* (5.5 mol %) under a N_2 atmosphere in the presence of LiHMDS (1.5–5 mmol) and LiI (0.1 mmol) in THF (3 mL) at −20 °C for 12 h; Isolated products; Ee values were determined by HPLC using chiral Daicel columns. [b]The reaction was conducted at 0 °C.

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in 93% yield and 94% ee. In addition, we applied an alkyl substituted dithiane (R = *i*-Pr) in the above asymmetric catalytic reaction. However, the reaction could not occur at all.

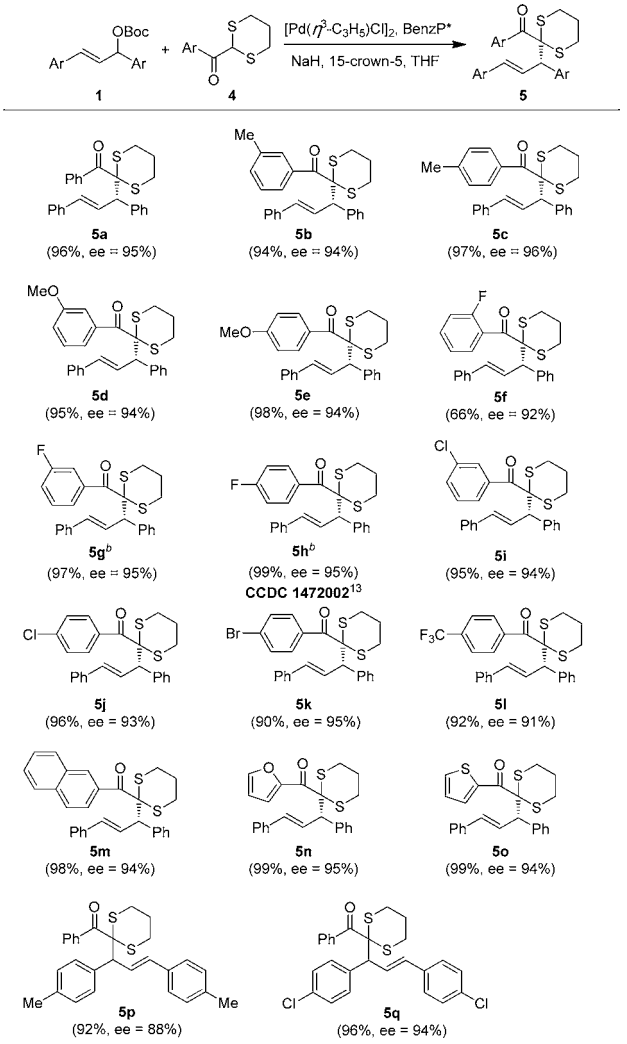
With the most promising results being obtained in the Pd-catalyzed asymmetric substitution with 2-aryl-1,3-dithianes **2** as acyl anion equivalents, 2-aroyl-1,3-dithianes **4** containing an additional carbonyl group were then used in place of **2** in the above reaction. After examining the effects of the ligand and base, we found that a catalytic system consisting of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and BenzP* was also effective in this case and the reaction proceeded smoothly in the presence of NaH and 15-crown-5 in THF at room temperature.[14] Under the optimum reaction conditions, a series of 2-aroyl-1,3-dithianes **4** were allowed to react with **1b** (Scheme 3). We were pleased to find that almost all alkylated products could be obtained with excellent yields and enantioselectivities regardless of the electronic nature of the aryl ring (**5a**−**5o**). Only product **5f** was obtained in a somewhat lower yield. Furthermore, allyl substrates with both Me and Cl groups at para-positions of the phenyl rings were screened with **5p** and **5q** being obtained in excellent catalytic behaviors.

To prove the usefulness of this new synthetic methodology, the reaction of **1b** with **2a** was performed on a gram scale with the above optimized reaction conditions (Scheme 4). The desired product **3a** was obtained in high yield (1.48 g, 95%) with excellent enantioselectivity (96% ee). The derivatization of **3a**, including the conversion of the 1,3-dithiane moiety into a carbonyl group using oxidative desulfurization and a methylene group via reductive desulfurization, was examined. Thus, compound **6** was obtained in high yield via the desulfurization of product **3a** using *N*-iodosuccinimide (NIS) as an oxidizing agent in a mixed solvent system of MeCN and H_2O. The enantioselectivity remained unaltered (Scheme 2).[8a] Alternatively, **3a** could also be converted to the reductive desulfurization product **7** by sulfur−hydrogen exchange in the presence of Raney-Ni in ethanol.[16]

2,4,6-Triphenyl-1-hexene (**9**), isolated from the starfish *Pteraster militaris*,[17a] metabolites of *Phellinus pini*, a fungus pathogenic to conifer trees,[17b] and rhizomes of *Begonia nantoensis*,[17c] could be synthesized from **5a** via compound **8** as an intermediate with ease (Scheme 5). Thus, by treating **5a** with Raney-Ni in ethanol, compound **8** was prepared in 86% yield and 93% ee. Subsequently, compound **8** could be further converted to (*R*)-2,4,6-triphenyl-1-hexene (**9**) via the Wittig reaction in 94% yield and 90% ee. To the best of our knowledge, this is the first asymmetric synthesis of compound **9**.

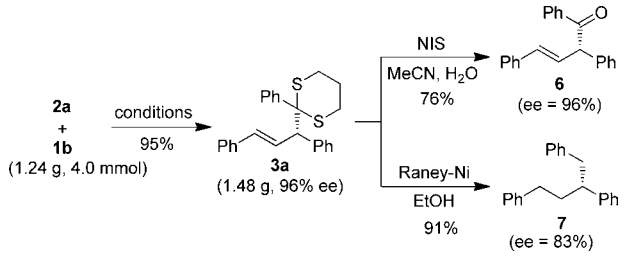
In summary, we have developed a Pd-catalyzed asymmetric allylic substitution with 1,3-dithianes as acyl anion equivalents. Under the optimal reaction conditions, the desired products can be obtained in high yields and with up to 96% ee. A gram scale synthesis has been achieved, and the corresponding alkylated products can be easily converted into several biologically active products. Our current work provides an alternative strategy that utilizes electrophilic carbonyl com-

Scheme 3. Scope of Substrates[a]

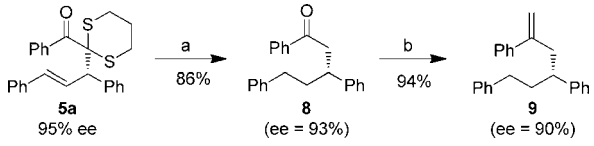


[a]Unless otherwise noted, the reaction of **1** (0.15 mmol) with **4** (0.1 mmol) was carried out using a catalytic system consisting of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) and BenzP* (5.5 mol %) under a N_2 atmosphere in the presence of NaH (0.15 mmol) and 15-crown-5 (0.12 mmol) in THF (4 mL) at room temperature for 12 h. Isolated products; ee values were determined by HPLC using chiral Daicel columns. [b]*t*-BuONa (0.15 mmol) was used in place of NaH.

Scheme 4. Gram Scale Synthesis of 3a and Its Transformation



Scheme 5. Derivatization of 5a[a]



[a]Reaction conditions: (a) Raney-Ni , EtOH; (b) Ph_3PMeBr, *n*-BuLi, THF, −40 °C to rt.

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pounds as nucleophilic species in Pd-catalyzed allylic substitution reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03161.

Experimental procedures, characterization details, and additional data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dlliu@sjtu.edu.cn.
*E-mail: wanbin@sjtu.edu.cn.

ORCID

Wanbin Zhang: 0000-0002-4788-4195

Notes

The authors declare no competing financial interest.
[§]Visiting professor of Shanghai Jiao Tong University from Chiba University (Japan).

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