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P(*i*-PrNCH$_2$CH$_2$)$_3$N: an efficient catalyst for TMS-1,3-dithiane addition to aldehydes

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ABSTRACT

Herein we report the use of commercially available P(*i*-PrNCH$_2$CH$_2$)$_3$N (**1a**) as an efficient catalyst for 2-trimethylsilyl-1,3-dithiane (TMS–dithiane) addition to aldehydes at room temperature. The catalyst loading required for these reactions (5 mol %) is the lowest recorded in the literature, and the majority of the reaction times for this transformation are the shortest thus far reported. A variety of functional groups are tolerated on the aryl aldehyde substrates.

1. Introduction

The addition of 1,3-dithiane (a masked acylcarbanion) to various electrophiles (e.g., aldehydes, ketones, and alkyl halides) is one of the most practiced methodologies in synthetic organic chemistry for the formation of C–C bonds.[1–6] Also known as an 'umpolung', 'dipole inversion', or 'inversion of reactivity' reaction, this process at the SCS carbon of the dithiane allows facile generation of a carbonyl functionality under mild oxidation conditions using reagents such as $Hg(ClO_4)_2$, $CuCl_2$/CuO, $AgNO_3$, $Tl(NO_3)_3$,and [bis(trifluoroacetoxy)iodo]benzene.[6–10] The most common deprotonating agent for converting a 1,3-dithiane to a nucleophile for addition to an electrophilic carbon center is the use of a stoichiometric amount of BuLi.[1–6]

Umpolung of a dithiane for its addition to ketones and aldehydes has also been accomplished via catalytic activation of a silyl group in a 2-silyl-1,3-dithiane.[11–14] Thus Pollicino and co-workers reported the use of a stoichiometric amount of cesium fluoride as a base in DMF solvent using 2-trimethylsilyl-4,6-dimethyl-1,3-dithiane and benzaldehyde to obtain a product yield of 72%, but the substrate scope was limited to benzaldehyde.[11] Corey and co-workers utilized an equivalent of CsF in a 1:1 mixture with CsOH at 0 °C for 2 h for the reaction of *p*-methoxybenzaldehyde with TMS–dithiane, which achieved a product yield of 85%.[12] A catalytic amount (10 mol %) of the fluoride ion source [*n*-Bu$_4$N][Ph$_3$SiF$_2$] was reported by DeShong and co-workers to achieve a 96% yield of product from the reaction of benzaldehyde (the only substrate tested) with TMS–dithiane.[13] Very recently, Mukaiyama and Michida reported that the use of 30 mol % of [*n*-Bu$_4$N][OPh] as a general catalyst for promoting the addition of TMS–dithiane at 0 °C in DMF to aldehydes and ketones, providing product yields of 60–97% and 63–93%, respectively.[14] This significantly improved methodology does, however, require a highly polar aprotic solvent and a high mol % of catalyst.[14]

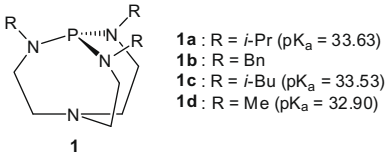

Figure 1. Proazaphosphatrane **1**.

We have found[15] that proazaphosphatranes such as those shown in Figure 1 are strongly basic, possessing pK_a values in the range 32–34 in MeCN for their P-protonated N_{basal}→P transannulated conjugate acids.[16] To the extent that N_{basal}→P transannulation may be occurring during reactions catalyzed by **1**, the nucleophilicity of the phosphorus may be enhanced.[15b] We previously reported reactions in which proazaphosphatranes can activate silicon functionalities,[17–23] as for example in the silylation of alcohols using *tert*-butyldimethylsilyl chloride,[17,18] the synthesis of cyanohydrins via the addition of a trialkylsilylcyanide to carbonyl compounds,[19,20] the desilylation of TBDMS ethers,[21] and the nucleophilic aromatic substitution of aryl fluorides with aryl silylethers.[22,23]

Because proazaphosphatranes can activate silicon functional groups[17–23] in addition to functioning as strong Lewis bases,[15,16] it occurred to us that in view of the paucity of reports in which the catalytic activation of TMS–dithiane for carbonyl umpolung[13,14] has been utilized, proazaphosphatranes might function well in such reactions. Here we report the use of a proazaphosphatrane as an efficient catalyst for 1,3-dithiane addition to the carbonyl of aldehydes as shown in Scheme 1.

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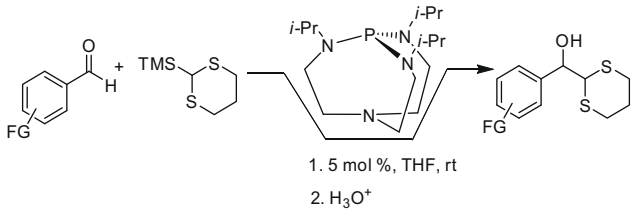


Scheme 1. General reaction scheme.

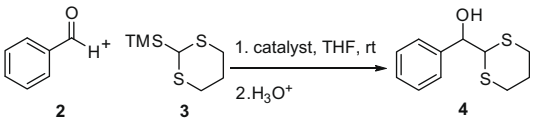
2. Results and discussion

For optimization studies (Table 1) we chose the reaction of an electron-neutral aldehyde (**2**) with TMS–dithiane (**3**). Using 2 mol % of **1a**, the isolated yield of product **4** was only 52% (entry 1). Increasing the catalyst loading to 5 mol %, however, augmented that yield to 98% (entry 2) over the same time period. Gratifyingly, this reaction time could be shortened to 30 min without compromising yield (entry 3). The conditions of entry 3 for proazaphosphatranes **1b–d** also gave excellent yields of product **4** (Table 1, entries 4–6). Proazaphosphatrane **1a** was our catalyst of choice, however, because of the combination of its superior performance, commercial availability,[24] and ease in handling owing to its crystalline nature when purified by sublimation.[25] It is noteworthy that our catalyst loading of 5 mol % is the lowest recorded in the literature for this methodology. According to NMR spectroscopy, no reaction was observed in the absence of catalyst (entry 7).

With the conditions in entry 3 of Table 1, a variety of aldehydes were screened to generalize the scope of catalyst **1a** (Table 2). Electron-donating groups such as methoxy (entry 1) and methyl (entry 2) resulted in excellent isolated product yields. Electron-withdrawing and acid-sensitive groups such as ester (entry 3) and cyano (entry 4) gave excellent and good yields, respectively. A halogen-containing aryl aldehyde (entry 5) and an enolizable aliphatic aldehyde (entry 6) provided excellent product yields. With the sterically congested aldehyde 2-biphenyl carboxaldehyde (Table 2, entry 7) a good isolated yield of product (81%) was realized.

Because only two heterocyclic aldehydes were previously examined in this reaction,[14] we examined five five- and two six-membered ring examples with our protocol, in which the low catalyst loading of 5 mol % was maintained. The oxygen-containing benzofuran-2-carboxaldehyde participated well in its reaction with dithiane (Table 2, entry 8) as did the halogenated nitrogen heterocycle in entry 9 and the N- and S-containing heterocycle in

Table 1
Survey of proazaphosphatranes (**1**)[a]

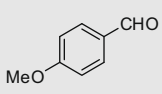
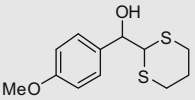
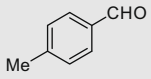
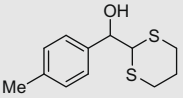
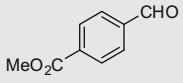
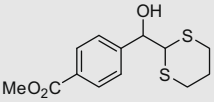
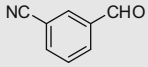
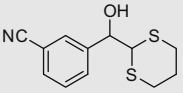
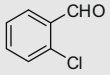
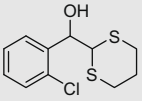
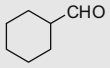
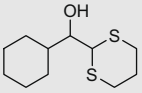
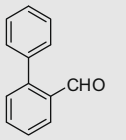
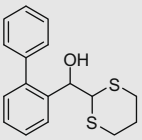
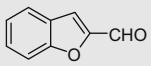
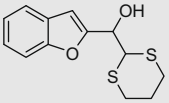
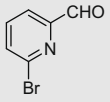
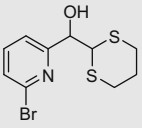
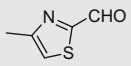
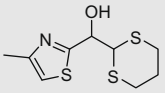
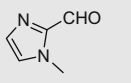
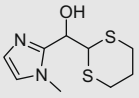
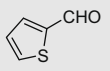
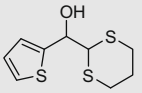
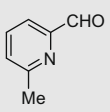
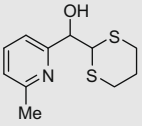
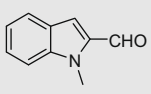
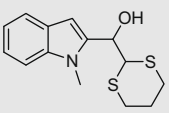


2 **3** **4**

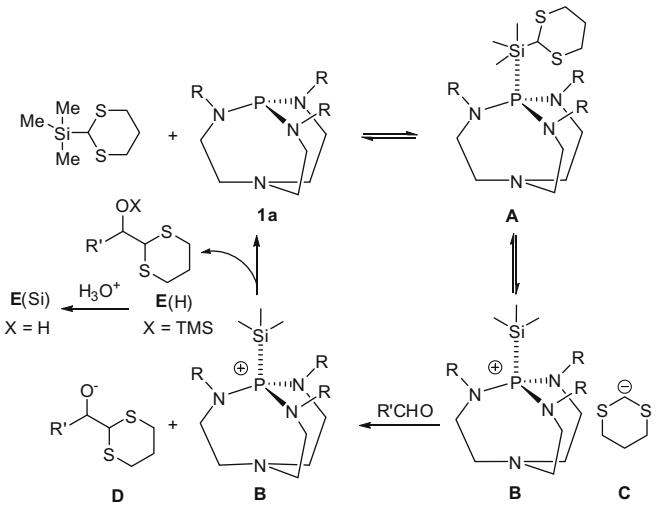
Entry	Catalyst	Mol %	Time	Yield of **4**[b] (%)
1	**1a**	2	24 h	52
2	**1a**	5	24 h	98
3	**1a**	5	30 min	98[d] (96)[c]
4	**1b**	5	30 min	95[d]
5	**1c**	5	30 min	97[d]
6	**1d**	5	30 min	95[d]
7	None	—	24 h	0

[a] Reaction conditions: catalyst (*x* mol %), benzaldehyde (2.0 mmol), 3 (2.4 mmol), THF (2 mL), rt followed by 1 N HCl (3 ml).
[b] Isolated yield after column chromatography.
[c] Lit. yield see Refs. 13,14.
[d] Averages of three runs.

Table 2
Reaction scope of aldehydes with 2-trimethylsilyl-1,3-dithiane catalyzed by **1a**[a]

Entry	Aldehyde	Product	Yield[b] (%)
1			95 Lit.: 85[c],95[d]
2			98 Lit.: 97[d]
3			93
4			80
5			96 Lit.: 95[d]
6			94 Lit.: 83[d]
7			81
8			95
9			92
10			94
11			67
12			97
13			98
14			94

[a] Reaction conditions: aldehyde (2 mmol), 3 (2.4 mmol), THF (2 mL), **1a** (5 mol %), rt, 30 min followed by 1 N HCl (3 mL).
[b] Isolated yield after silica gel column chromatography.
[c] See Ref. 12.
[d] See Ref. 14.



Scheme 2. Proposed mechanism for TMS-1,3-dithiane addition reactions of aldehydes catalyzed by **1a**.

entry 10; all giving excellent product yields. Although the heterocycle containing two nitrogens shown in entry 11 gave a rather moderate yield of product, excellent product yields were achieved with thiophene-2-carboxaldehyde (entry 12), 6-methyl-2-pyridinecarboxaldehyde (entry 13), and N-methylindole-2-carboxaldehyde (entry 14).

From the variety of aldehydes included in the scope of our protocol, it appears that our methodology is general for those possessing electron-withdrawing or -donating groups and also for acid- or base-labile functional groups. Heterocyclic and enolizable aliphatic aldehydes are also amenable to our protocol.

A proposed mechanism for the addition of TMS–dithiane to aldehydes under our conditions is depicted in Scheme 2. Initially, **1** forms a pentacoordinated silicate TMS–dithiane adduct **A** which enriches the electron density on the silicon, consequently weakening the bonds around this atom and thus favoring ionization to species **B** and **C**. Thereafter, the dithiane anion **C** nucleophilically attacks the aldehyde carbon giving **D**, which then nucleophilically attacks cation **B** giving intermediate **E**(Si). This intermediate is subsequently hydrolyzed in a second step to give the product **E**(H) with regeneration of the catalyst **1a**.

In summary, we find that the nonionic strongly Lewis basic proazaphosphatrane **1a** is an efficient catalyst for the addition of 2-trimethylsilyl-1,3-dithiane to aldehydes. To the best of our knowledge, our catalyst loading for the synthesis of β-hydroxydithianes using a TMS–dithiane reagent is the lowest reported in the literature. Our protocol operates efficiently at room temperature in 30 min with a commercially available catalyst, and product yields are generally excellent. Compared with literature reports of the highest yields for five products shown in Tables 1 and 2, our methodology gave a substantially higher yield in one instance and equal yields (within 1%) in the remaining 4 cases.

3. Experimental

3.1. General reaction procedure

A round-bottomed flask was charged with **1** (0.1 mmol, 5 mol %) in a nitrogen-filled glove-box. To this was added 2.0 mL of anhydrous tetrahydrofuran (THF) followed by the addition of aldehyde (2.0 mmol) at room temperature. The resulting solution was stirred at room temperature for 15 min and then 2-trimethylsilyl-1,3-dithiane **3** (2.4 mmol) was added over a period of two min. Progress of the reaction was monitored by proton NMR spectroscopy. The reaction mixture was stirred for 30 min followed by quenching with 3 mL of an aq solution of 1 N HCl. The mixture was stirred for an additional 1 h and then it was neutralized with saturated aq $NaHCO_3$ solution followed by extraction with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography using 30% EtOAc/hexane as eluent, whereas in the case of entry 11 of Table 2, 20% (v/v) $MeOH/CH_2Cl_2$ was employed.

Acknowledgments

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Supplementary data

Supplementary data (complete experimental details, references to known compounds, copies of ^1H and ^{13}C NMR spectra for all products, and HRMS reports for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.010.

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