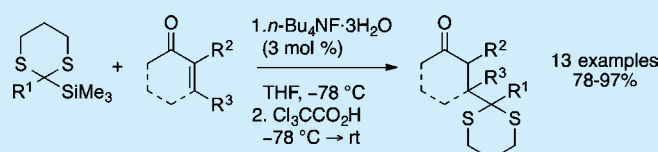


Catalytic Conjugate Addition of Acyl Anion Equivalents Promoted by Fluorodesilylation

Scott E. Denmark* and Lindsey R. Cullen

Roger Adams Laboratory, Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, Illinois 61801, United States

S Supporting Information



ABSTRACT: The conjugate addition of acyl anion equivalents derived from 2-silyl-1,3-dithianes to α,β -unsaturated ketones and esters has been achieved using a substoichiometric amount of TBAF. High yields and short reaction times are observed for the addition of aryl-1,3-dithianes to a variety of cyclic and acyclic α,β -unsaturated carbonyl acceptors. Observation of the reactive anion by ^{13}C NMR spectroscopy and extension to an asymmetric variant is also presented.

The natural reactivity pattern of carbonyl compounds leads to the ready construction of consonant or odd functional group relationships. To access dissonant or even relationships with carbonyl compounds requires charge-affinity inversion or *umpolung*.^{1a} A classic application of this concept concerns the construction of 1,4-dicarbonyl compounds.^{1b} In this case, a new carbon–carbon bond can be formed by inducing an electrophile (aldehyde) to react as a nucleophile at the carbonyl carbon (acyl anion) with α,β -unsaturated carbonyl acceptors. The prevalence of the 1,4-dicarbonyl motif in natural products,^{1c,d} as well as their pivotal role in the construction of aromatic heterocycles,^{1e–g} has stimulated the development of methods for their construction.

Current approaches to the synthesis of 1,4-dicarbonyl compounds include transition-metal hydroacylation,² acyl radical additions,³ and *umpolung* based methods.^{1a} Classical *umpolung* methods focus on derivatization of an aldehyde to an acyl anion equivalent (e.g., 1,3-dithiane,⁴ cyanohydrin⁵), followed by stoichiometric deprotonation using a strong base. Conjugate addition of these organolithium species to α,β -unsaturated acceptors is often plagued by competitive 1,2-addition. High selectivity for the 1,4-addition product requires use of stoichiometric additives such as HMPA^{6a} or copper salts^{6b} or more stabilized anionic equivalents.^{6c} More recently, the Stetter reaction has been developed as an alternative method for the *catalytic* generation of acyl anion equivalents under mild conditions using NHC catalysts.⁷ Despite significant development, the Stetter reaction still suffers from limitations because of the lower nucleophilicity of the Breslow intermediate.^{7d} Most methods require activated acyclic Michael acceptors (i.e., alkylidene malonates, nitroalkenes, etc.) and are particularly sensitive to steric effects. Additions to simple cyclic acceptors are rarely reported.^{7e}

To expand the scope of acyl anion chemistry, a research program was initiated for the *catalytic* generation of acyl anion

equivalents using fluorodesilylation.^{8a–c} Generation of nucleophiles by catalytic fluorodesilylation has been successful in a variety of contexts, including carbonyl allylation,^{8d} alkynylation,^{8e} trifluoromethylation,^{8f} and Mukaiyama aldol reactions.^{8g} These methods are operationally simple and use readily available quaternary ammonium fluoride salts (e.g., TBAF) as catalysts. The method reported herein extends fluorodesilylation to the reaction of sulfur-stabilized high $\text{p}K_{\text{a}}$ anions as acyl anion equivalents.⁹ Similar to the Stetter reaction, this method is catalytic but retains the high reactivity of stoichiometric lithio-acyl anion equivalents, allowing for the addition of acyl anions to less reactive, cyclic Michael acceptors. Additionally, the products derived from this method are partially protected, allowing differentiation between the two carbonyl moieties.

Initial investigation focused on the conjugate addition of (trimethylsilyl)phenyldithiane (**1a**) to 2-cyclohexenone (**2a**) promoted by a substoichiometric amount of tetrabutylammonium fluoride trihydrate (Table 1). Gratifyingly, exclusive 1,4-addition was observed for this reaction. The amount of silyldithiane was important because of partial quenching of the active carbanion by the water introduced from TBAF. An equimolar ratio of silyl dithiane to enone resulted in only moderate yields of **3a** (entry 1) due to competitive addition of the intermediate enolate (*ii*, see Scheme 2) to **2a**. A slight excess of dithiane **1a** (1.5 equiv) resulted in nearly quantitative conversion to the desired product after 30 min at $-78\text{ }^{\circ}\text{C}$ (entry 2). Increasing the quantity of **1a** further was not beneficial (entry 3). To our surprise, the loading of fluoride could be reduced as low as 0.5 mol % (entries 4–7) with no impact on the yield. This is especially advantageous for the potential application of chiral, nonracemic, quaternary ammonium fluoride catalysts.

Received: October 22, 2013

Published: December 11, 2013

Table 1. Optimization of Silyl Phenyl Dithiane Addition^a

entry	equiv of 1a ^b	equiv of TBAF (mol %)	yield ^c (%)
1	1.0	10	58
2	1.5	10	94
3	2.0	10	91
4	1.5	5	92
5	1.5	2.5	96
6	1.5	1	91
7	1.5	0.5	96

^aAll reactions were performed on a 0.25 mmol scale in THF [0.08 M] at -78°C for 30 min, followed by quenching with 2 M $\text{Cl}_3\text{CCO}_2\text{H}$ in THF. ^bEquivalents based upon 2a. ^cIsolated yield of chromatographically homogeneous material.

With optimized conditions in hand, the conjugate addition of arylsilyldithianes (1a–c) to a variety of α,β -unsaturated carbonyl acceptors (2a–l) was explored (Table 2). Excellent yields were obtained for additions to cyclic enones, including five- and seven-membered rings (3b and 3c, respectively). In view of the high reactivity of the intermediate anion, sterically encumbered enones (3d and 3e) were also viable substrates, although extended reaction times or elevated temperatures were necessary. The addition to (*R*)-carvone proceeded with excellent yield, although 3f was obtained as a mixture of diastereomers. Additions to acyclic (3g) and benzo-fused (3h) enones proceeded uneventfully, and enoate substrates such as coumarin (3i) and methyl cinnamate (3j) were also reactive, albeit requiring longer reaction times. Electron-poor (1b) and

2-substituted (1c) arylldithianes also participated. The corresponding aldehydes of these substrates are nonoptimal substrates in the analogous Stetter reaction.

A number of α,β -unsaturated carbonyl acceptors did not participate successfully under the optimized reaction conditions (Figure 1). Competitive 1,2-addition was observed for α,β -unsaturated ester 5 and aldehyde 6, and the optimized reaction conditions resulted in recovered starting material.¹⁰ Highly electrophilic acceptors 7 and 8, which are effective substrates for Stetter reactions, are unreactive because of the inability of the stabilized metallo-ketenimine or enolate anions to desilylate the starting silyl dithiane. This may allow for chemoselective reactions of multi acceptor-containing substrates which are not possible with current methods. The reactive acyl anion is also significantly basic ($\text{p}K_{\text{a}} \sim 30$) and methyl enones such as 9 undergo enolization to the corresponding silyl enol ethers.

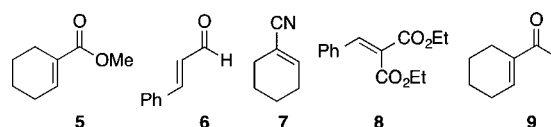
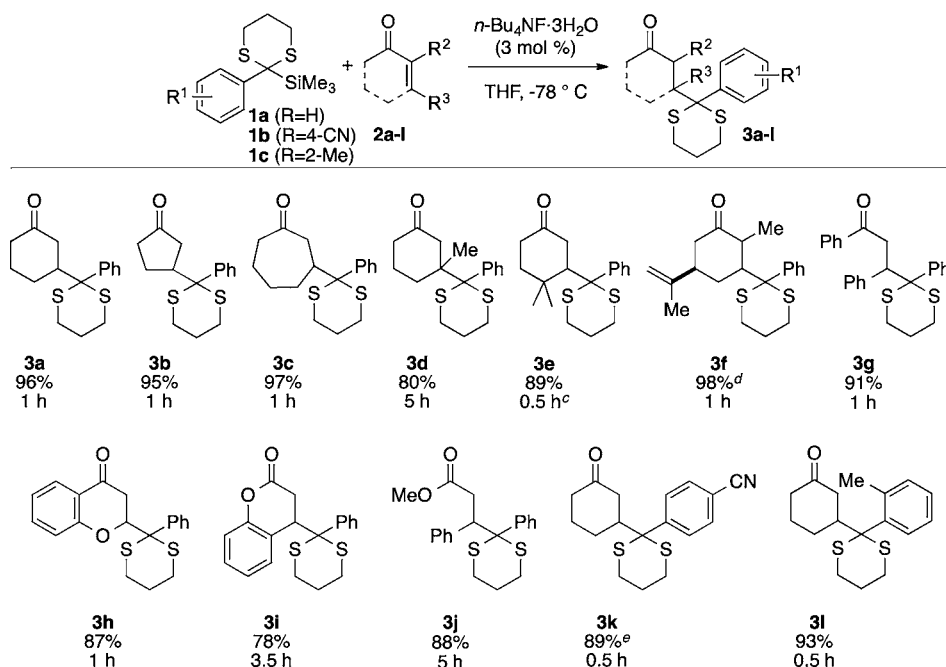


Figure 1. Unsuccessful Michael acceptors.

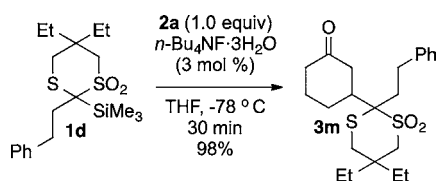
Attempts to extend this method to alkylsilyldithiane substrates met with difficulty. The increase in $\text{p}K_{\text{a}}$ for alkylldithianes resulted in enolization of 2a. Conjugate addition may be favored by increasing the stabilization of the anion by partial oxidation of the dithiane moiety. Thus, monosulfone substrate 1d was prepared.¹¹ The 4,4-diethyl variant of the dithiane was employed to suppress deprotonation at C(3). Gratifyingly, reaction of 1d with 2a under the optimized reaction conditions led to exclusive 1,4-addition (Scheme 1) to

Table 2. Reaction Scope of Aryl 2-Silyl-1,3-dithiane Conjugate Addition^{a,b}

^aAll reactions were performed on a 1.0 mmol scale of 2 with 1.5 equiv of 1 in THF [0.08 M] at -78°C , followed by quenching with 2 M $\text{Cl}_3\text{CCO}_2\text{H}$ in THF. ^bYields refer to chromatographically homogeneous, isolated products. ^cReaction performed at 0°C . ^dYield refers to a mixture of three diastereomers. ^eYield of recrystallized material after column chromatography.

give differentially protected 1,4-diketone **3m** in near-quantitative yield.

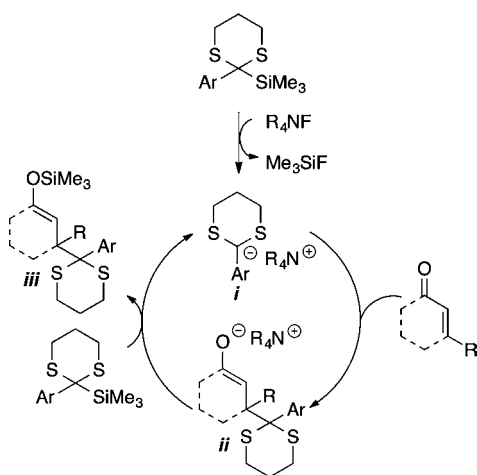
Scheme 1. Application to Alkyl Acyl Anion Surrogates^a



^aSee the Supporting Information for experimental details.

The proposed catalytic cycle is initiated by fluorodesilylation of the 2-silyldithiane to generate a sulfur-stabilized dithianyl anion (*i*) (Scheme 2). Conjugate addition of this anion to an α,β -unsaturated carbonyl compound results in the generation of an ammonium enolate (*ii*), which then regenerates the reactive dithianyl anion by silylation to form the silyl enol ether (*iii*) of the 1,4-adduct. Acidic workup of the reaction furnishes the conjugate addition product as a masked 1,4-dicarbonyl compound. Thus, this process is initiated by fluoride but the enolate is responsible for catalytic turnover. Because the quaternary ammonium counterion is conserved throughout the cycle, the possibility for asymmetric induction using a chiral, nonracemic ammonium fluoride salt becomes apparent.

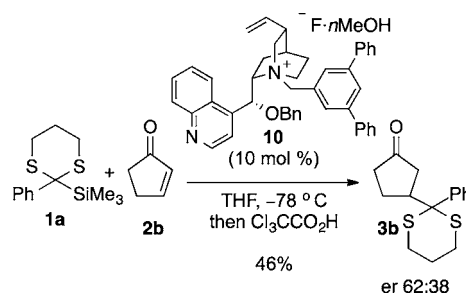
Scheme 2. Proposed Mechanism of Catalytic Conjugate Addition of Dithianyl Anions



Accordingly, chiral, nonracemic ammonium fluoride catalysts based upon the cinchona alkaloid scaffold were examined. Fluoride catalyst **10** was prepared from the corresponding quaternary ammonium bromide salt by ion exchange chromatography. The salt was obtained as a stable, free-flowing, hygroscopic powder when isolated as a methanol solvate (see the Supporting Information for details). Although catalyst **10** effected the 1,4-addition for a variety of substrates, only modest enantioenrichment was evident (Scheme 3). Optimization of the chiral catalyst is ongoing.

Finally, the structure of the dithianyl nucleophile was probed using ¹³C NMR spectroscopy to distinguish a free anion from a hypervalent silicate species. Initial attempts to observe the ion pair with the standard fluoride catalyst (TBAF·3H₂O) proved unsuccessful because of rapid protonation of the anion by water. The anhydrous fluoride source, TAS-F (tris-

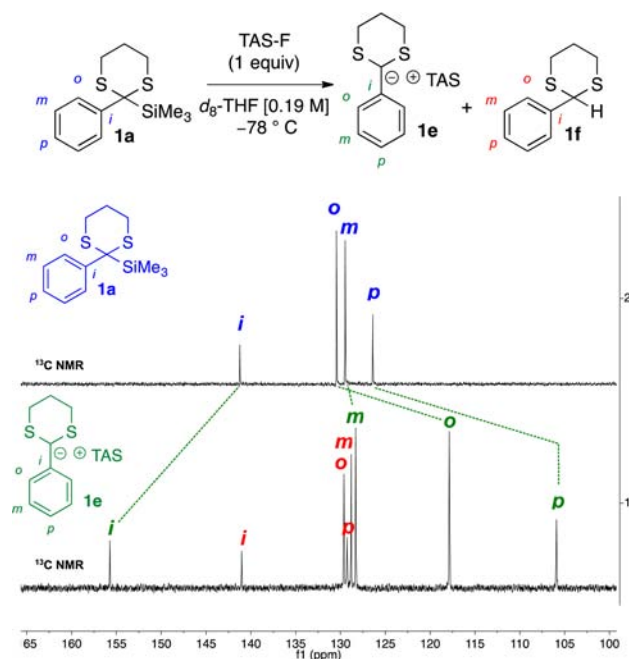
Scheme 3. Conjugate Addition Utilizing Chiral Fluoride Catalyst^a



^aSee the Supporting Information for experimental details.

(dimethylamino)sulfonium difluorotrimethylsilicate), previously used by Reich et al. was more successful.¹² The dramatic changes in the chemical shifts observed indicate significant charge delocalization into the benzene ring (Scheme 4). The upfield shifts in the *ortho* and *para* carbon signals (indicated by green lines) match the similar carbon shifts for the HMPA-solvent separated 2-lithio-2-phenyldithiane (117.5 ppm and 104.1 ppm, respectively)¹³ providing strong evidence that this reaction proceeds through an ion-pair intermediate.

Scheme 4. ¹³C NMR Spectroscopic Observation of Dithianyl Anion^a



^aReaction performed on a 0.13 mmol scale in a 5-mm NMR tube in THF-*d*₈ [0.19 M] at -78 °C.

In conclusion, the addition of acyl anion equivalents to unactivated α,β -unsaturated ketones and esters using a fluorodesilylation strategy has been developed. This method is operationally simple and uses a readily available quaternary ammonium fluoride salt as the catalyst. The masked 1,4-diketone products were obtained in excellent yields and with short reaction times. This method is complementary in scope to existing methods for the synthesis of 1,4-dicarbonyl compounds. Preliminary results are promising in the expansion

of scope to alkyl-acyl anion equivalents as well as for development of an asymmetric variant.

■ ASSOCIATED CONTENT

■ Supporting Information

Full experimental procedures, analyses, characterization data, and NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sdenmark@illinois.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the W. M. Keck Foundation for generous financial support.

■ REFERENCES

- (1) (a) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239. (b) Lever, O. W., Jr. *Tetrahedron* **1976**, *32*, 1943. (c) Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (e) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867. (f) Graening, T.; Thrun, F. Furans and their Benzo Derivatives: Synthesis. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008; Vol. 3, pp 497–569. (g) Bergman, J.; Janosik, T. Five-Membered Heterocycles: Pyrrole and Related Systems. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; Vol. 4, pp 269–275.
- (2) For recent reviews, see: (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (b) Lueng, J. C.; Krische, M. J. *Chem. Sci.* **2012**, *3*, 2202.
- (3) For relevant reviews, see: (a) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377. (b) Chatgililoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.
- (4) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed.* **1965**, *4*, 1077.
- (5) For a review, see: Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.
- (6) (a) Brown, C. A.; Yamaichi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 100. (b) Mukaiyama, T.; Narasaka, K.; Furusato, M. *J. Am. Chem. Soc.* **1972**, *94*, 8641. (c) Ager, D. J.; East, M. B. *J. Org. Chem.* **1986**, *51*, 3983.
- (7) (a) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407. For recent reviews, see: (b) de Alaniz, J. R.; Rovis, T. *Synlett* **2009**, 8, 1189. (c) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (d) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55. For a rare example of an intermolecular Stetter reaction with a cyclic acceptor, see: (e) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872.
- (8) For relevant reviews, see: (a) Gawronski, J.; Wascinska, N.; Gajewy, J. *Chem. Rev.* **2008**, *108*, 5227. (b) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (c) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526. For selected examples, see: (d) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, *19*, 3043. (e) Bohsako, A.; Asakura, C.; Shioiri, T. *Synlett* **1995**, 1033. (f) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3707. (g) Ooi, T.; Doda, K.; Maruoka, K. *Org. Lett.* **2001**, *3*, 1273.
- (9) For limited examples of the reactivity of 2-silyl-1,3-dithianes toward alternative electrophiles, see: (a) Grotjahn, D. B.; Andersen, N. H. *J. Chem. Soc., Chem. Commun.* **1981**, 306. (b) Andersen, N. H.; McCrae, D. A.; Grotjahn, D. B.; Gabhe, S. Y.; Theodore, L. J.; Ippolito, R. M.; Sarkar, T. K. *Tetrahedron* **1981**, *37*, 4069. (c) Michida, M.; Mukaiyama, T. *Chem.—Asian J.* **2008**, *3*, 1592. (d) Wadhwa, K.; Verkade, J. G. *Tetrahedron Lett.* **2009**, *50*, 4307.

(e) Capperucci, A.; Cerè, V.; Degl'Innocenti, A.; Nocentini, T.; Pollicino, S. *Synlett* **2002**, 1447.

(10) Under optimized conditions (3 mol % TBAF, THF, -78°C , 7 h) very poor conversion to the 1,2-adduct was observed (9%) for substrate **6**. Increased fluoride loading (10 mol % TBAF) allowed for full conversion of the starting material, yielded the 1,2-adduct in 80% yield. See the Supporting Information for full details. Addition of dithianyl nucleophiles to aromatic aldehyde acceptors is known to be promoted by a substoichiometric amount of a Lewis based additive; see ref 9c,d.

(11) Preparation adapted from the following precedent: (a) Carlson, R. M.; Helquist, P. M. *J. Org. Chem.* **1968**, *33*, 2596. (b) Gokel, G. W.; Gerdes, H. M.; Dishong, D. M. *J. Org. Chem.* **1980**, *45*, 3634. See the Supporting Information for details.

(12) Biddle, M. M.; Reich, H. J. *J. Org. Chem.* **2006**, *71*, 4031.

(13) For NMR studies of lithio-dithianes, see: (a) Abatjoglou, A. G.; Eliel, E. L.; Kuyper, L. F. *J. Am. Chem. Soc.* **1977**, *99*, 8262. (b) Juaristi, E.; Cruz-Sánchez, J. S.; Ramos-Morales, F. R. *J. Org. Chem.* **1984**, *49*, 4912. (c) Reich, H. J.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869.