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Isothiourea-Mediated Stereoselective *C*-Acylation of Silyl Ketene Acetals

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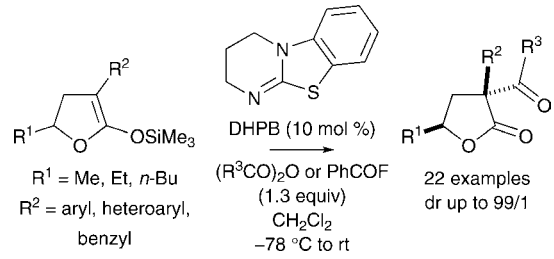
ABSTRACT



Isothiourea DHPB promotes the diastereoselective *C*-acylation of silyl ketene acetals with anhydrides or benzoyl fluoride, giving 3-acyl-3-aryl or 3-acyl-3-alkylfuranones in excellent yields and stereoselectivities (up to 99:1 dr).

Stereoselective methods for the *C*-acylation of enolates or their equivalents offer synthetic access to versatile building blocks in organic synthesis. While a number of catalytic asymmetric Steglich[1] and Black rearrangements[2] of heterocyclic carbonate derivatives have been developed that deliver *C*-carboxyl derivatives in high ee, few methodologies have been delineated that can effect the direct *C*-acylation of enolates.[3] Central to the problems associated with this transformation is the propensity for competitive *O*- and *C*-acylation processes, typically leading to mixtures of *O*- and *C*-acylated products.[4] Strategies to solve these issues such as Lewis acid promoted *C*-acylation of enolsilanes[5] or TBAF promoted *C*-acylation of silyl enol ethers[6] have been reported. As an alternative approach, Fu and Mermerian have elegantly shown that planar chiral PPY derivative **2** promotes the catalytic enantioselective *C*-acetylation of both cyclic and acyclic silyl ketene acetals bearing an α-aryl or α-alkenyl substituent with acetic anhydride.[7] Building upon this precedent, we proposed to identify a Lewis base[8] that would

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(1) Steglich, W.; Höfle, G. *Tetrahedron Lett.* **1970**, *11*, 4727–4730. For asymmetric versions of this reaction, see: Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533. Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369. Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925–934. Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769–772. Seitzberg, J. G.; Dissing, C.; Søtofte, I.; Norrby, P.-O.; Johannsen, M. *J. Org. Chem.* **2005**, *70*, 8332–8337. Busto, E.; Gotor-Fernández, V.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 2626–2632. For an asymmetric acetyl group rearrangement, see: Dietz, F. R.; Gröger, H. *Synthesis* **2009**, *24*, 4208–4218.

(2) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Org. Chem.* **1987**, *52*, 5425–5403. Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921–3924. Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14–15.

(3) Cyanoformates promote the direct *C*-carboxylation of enolates; for examples, see: Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428. Crabtree, S. R.; Alex Chu, W. L.; Mander, L. N. *Synlett* **1990**, 169–170.

(4) Caine, D. In *Carbon-Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1, pp 250−258.

(5) For example, see: Fleming, I.; Iqbal, J.; Krebs, E.-P. *Tetrahedron* **1983**, *39*, 841–846. Le Roux, C.; Mandrou, S.; Dubac, J. *J. Org. Chem.* **1996**, *61*, 3885–3887.

(6) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron Lett.* **2002**, *43*, 2945–2948.

(7) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051. Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604–5607. For a related reaction involving silyl ketene imines and anhydrides, see: Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949–952.

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lead to the efficient *C*-acylation of silyl ketene acetals[9,10] and to subsequently develop a general and highly diastereoselective version of this process for the preparation of stereodefined 3-acyl-3-aryl or 3-acyl-3-alkylfuranones **5** from silyl ketene acetals such as **4** (Figure 1). This methodology

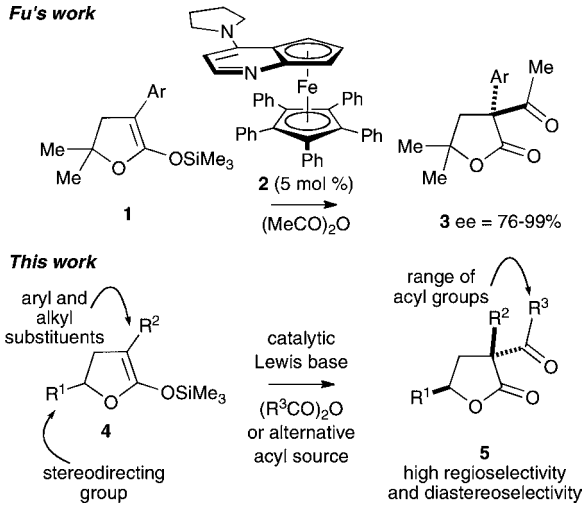


Figure 1. Proposed Lewis base promoted stereoselective *C*-acylation of silyl ketene acetals.

would be complementary to alternative approaches to these valuable building blocks such as the asymmetric alkylation or conjugate addition of 1,3-dicarbonyl species.[11]

Initial studies probed the effectiveness of a range of commercially available or readily prepared Lewis bases to promote the *C*-acylation of a model substrate, silyl ketene acetal **6**, with acetic anhydride. Under standardized conditions, amidines such as DBN **9**, DBU **10**, and dihydroimidazo[1,2-*a*]pyridine (DHIP) **11**, as well as *N*-methylimidazole (NMI) **12** and guanidine **13**,

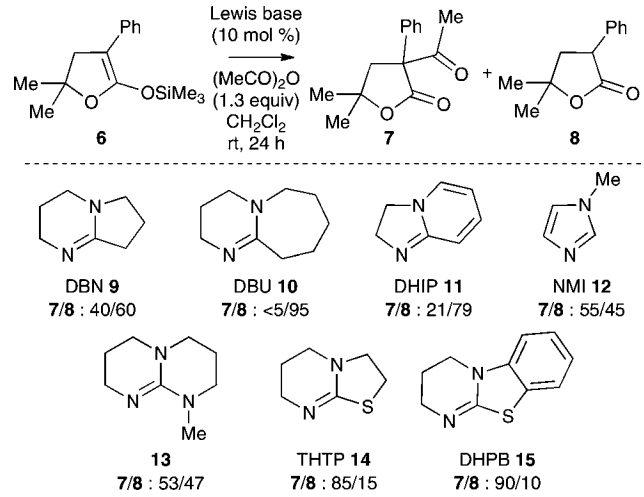
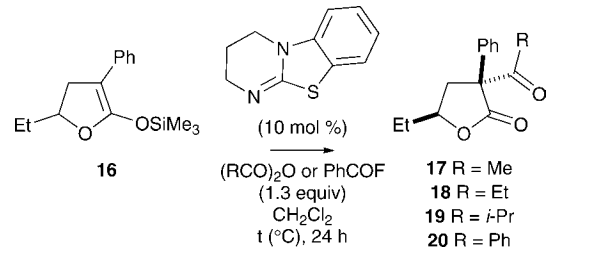


Figure 2. Screening Lewis base reactivity for the *C*-acylation of silyl ketene acetal **6** with acetic anhydride.

Table 1. Diastereoselective Isothiourea Promoted *C*-Acylation of Silyl Ketene Acetal **16**



entry	t (°C)	acyl source	R	dr	yield (%)
1	rt	$(MeCO)_2O$	Me	93/7	
2	0	$(MeCO)_2O$	Me	94/6	
3	−20	$(MeCO)_2O$	Me	95/5	
4	−40	$(MeCO)_2O$	Me	96/4	
5	−78 to rt	$(MeCO)_2O$	Me	98/2	78
6	−78 to rt	$(EtCO)_2O$	Et	97/3	78
7	−78 to rt	$(i\text{-}PrCO)_2O$	*i*-Pr	95/5	75
8	−78 to rt	PhCOF	Ph	>98/2	65

gave only modest conversions (<55%) to the desired *C*-acetyl product **7**, giving significant quantities of lactone **8**.[12] Further catalyst evaluation probed the use of isothioureas 2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyrimidine (THTP) **14** and 3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (DHPB) **15**, recently shown to be excellent *O*-acylation[13] and *C*-carboxyl transfer

(8) For a review of Lewis base mediated reaction processes, see: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.

(9) For the DMAP promoted *O*-benzoylation of silyl enol ethers with benzoyl fluoride and DMAP mediated *C*-benzoylation of silyl ketene acetals with benzoyl fluoride, see: Poisson, T.; Dalla, V.; Papamicaël, C.; Dupas, G.; Marsais, F.; Levacher, V. *Synlett* **2007**, 381–386.

(10) For examples of our previous research program concerned with applications of Lewis bases in organocatalysis, see: Thomson, J. E.; Rix, K.; Smith, A. D. *Org. Lett.* **2006**, *8*, 3785–3788. Thomson, J. E.; Campbell, C. D.; Concellón, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2008**, *73*, 2784–2791. Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. *Chem. Commun.* **2008**, 3528–3530. Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108–1113. Thomson, J. E.; Kyle, A. F.; Concellón, C.; Gallagher, K. A.; Lenden, P.; Morrill, L. C.; Miller, A. J.; Joannesse, C.; Slawin, A. M. Z.; Smith, A. D. *Synthesis* **2008**, 2805–2818. Concellón, C.; Duguet, N.; Smith, A. D. *Adv. Synth. Catal.* **2009**, *351*, 3001–3009. For a stoichiometric asymmetric oxindole synthesis promoted by a nitrone, see: Duguet, N.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2009**, *11*, 3858–3861.

(11) For examples of catalytic asymmetric alkylations of β-keto esters, see: Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879–7880. Ooi, T.; Miki, T.; Fukumoto, K.; Maruoka, K. *Adv. Synth. Catal.* **2006**, *348*, 1539–1542. For catalytic asymmetric Michael reactions of β-keto esters, see: Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241. Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4966–4970.

(12) We assume that lactone **8** arises as a result of hydrolysis of unreacted silyl ketene acetal upon exposure to air or moisture upon workup.

(13) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347–4350. Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37–40.

(14) For our previous work using DHPB as a catalyst for *O*- to *C*-carboxyl transfer, see: Joannesse, C.; Simal, C.; Concellón, C.; Thomson, J. E.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 2900–2907. For an asymmetric version of this reaction with chiral isothioureas, see: Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914–8918.

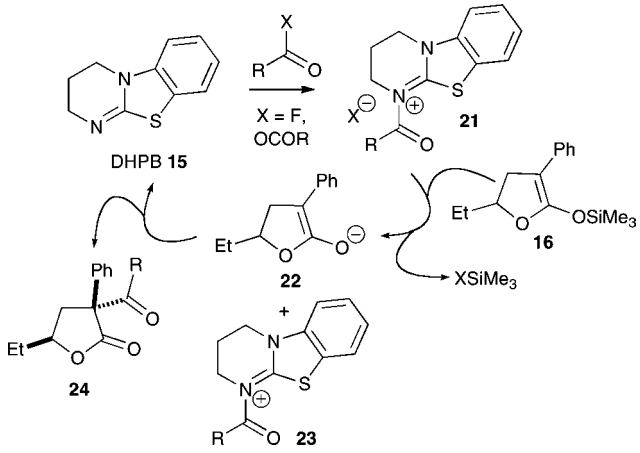


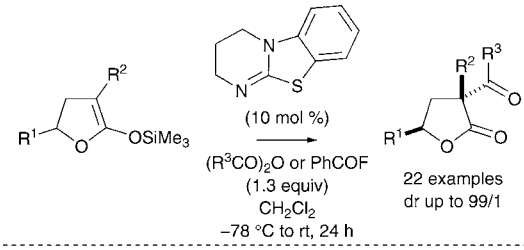
Figure 3. Proposed mechanism for the diastereoselective isothiourea promoted *C*-acylation of silyl ketene acetals.

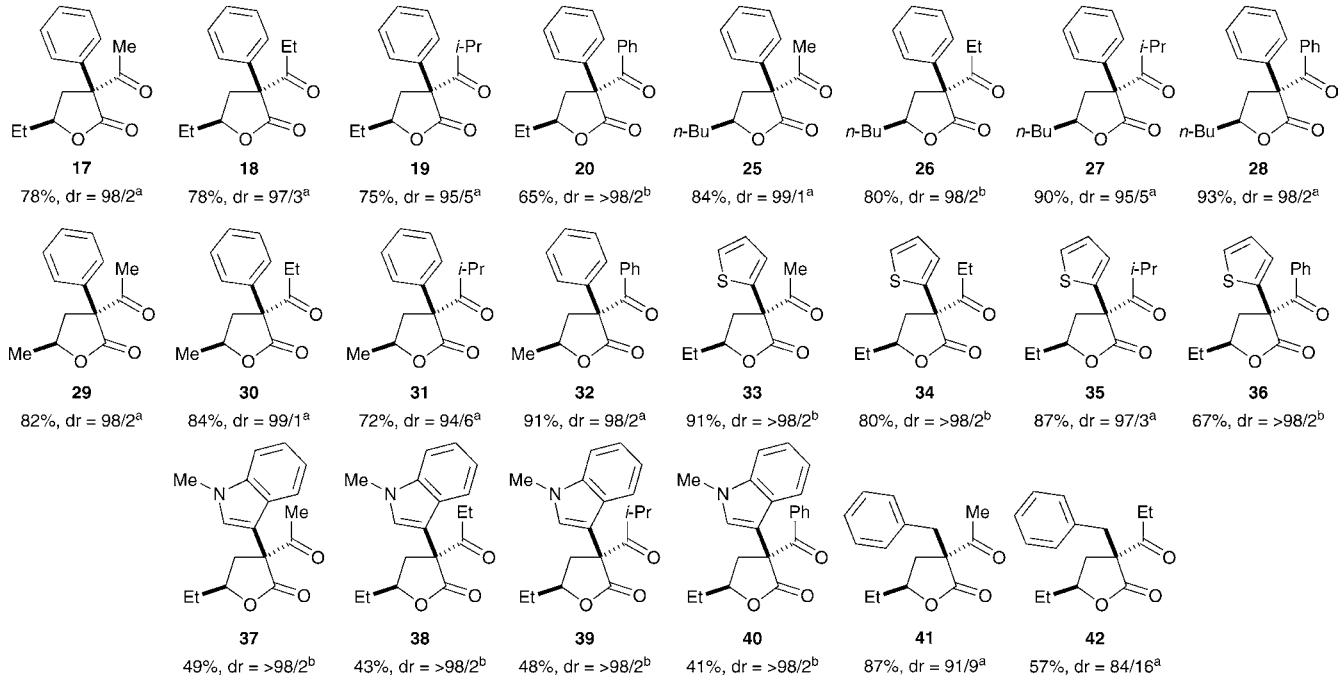
catalysts,[14] in this protocol. Both isothioureas gave markedly improved levels of *C*-acylation (>85% conversion to **7**), with isothiourea DHPB **15** showing the optimal conversion of the Lewis bases tested, giving *C*-acetyl **7** that was isolated in 90% yield (Figure 2).

Having identified isothiourea DHPB **15** as an efficient *C*-acetylation catalyst, the development of a general and stereoselective *C*-acylation protocol was investigated.[15] Treatment of silyl ketene acetal **16** with isothiourea **15** and acetic anhydride at rt proceeded to give *C*-acetyl **17** in excellent yield and with high stereoselectivity (dr = 93/7). Subsequent variation of reaction temperature gave optimal stereoselectivity, giving *C*-acetyl **17** in 98/2 dr, the relative configuration within which was confirmed by NOESY analysis.[16] This protocol proved equally applicable to alternative anhydrides, with propionic and isobutyric anhydride giving the corresponding *C*-acyl derivatives **18** and **19**, respectively, with excellent stereoselectivities (dr 97/3 and 95/5, respectively). The use of benzoyl fluoride in this reaction protocol was also developed, giving *C*-benzoyl **20** in excellent yield and stereoselectivity (dr >98/2) (Table 1).[17]

Consistent with Fu's proposal,[7] our current mechanistic hypothesis for this transformation requires initial formation of

Table 2. Scope of the DHPB Promoted Diastereoselective *C*-Acylation of Silyl Ketene Acetals





[a] Diastereomeric ratios were determined from inspection of the ^{1}H NMR spectra of the crude reaction mixtures. [b] Ratios were determined from the ^{1}H NMR spectra of the isolated products.

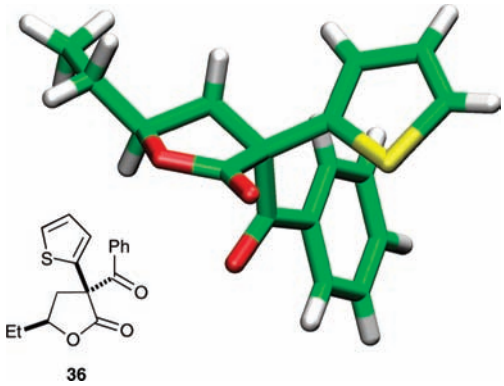


Figure 4. Molecular representation of the X-ray crystal structure of furanone **36**.

an activated acyl-isothiourionium ion **21** from the reaction of DHPB and the anhydride or benzoyl fluoride, with desilyation of the silyl ketene acetal promoted by either the carboxylate or fluoride counterion generating enolate **22**. Subsequent *C*-acylation of enolate **22**, *anti* to the stereodirecting C(5)-substituent,[18] generates the *C*-acyl product **24** with high diastereoselectivity and regenerates DHPB **15** (Figure 3).[19]

The scope of this protocol was next demonstrated, through variation of both the C(3)- and C(5)-substituents within the silyl ketene acetal, as well as the use of anhydrides and benzoyl fluoride as the acyl source.[20] Isothiourea DHPB promotes efficient *C*-acylation with C(3)-aryl and heteroaryl substitution, giving good to excellent levels of stereoselectivity in all cases (dr up to >98/2). C(5)-Methyl, ethyl, or *n*-butyl substituents all provide high levels of diastereocontrol (dr up to 99/1) in this reaction sequence. Notably, this protocol also tolerates C(3)-benzyl substitution, allowing acylation with acetic anhydride or propionic anhydride, generating lactones **41** and **42** in 87% and 57% yield and 91/9 and 84/16 dr, respectively (Table 2).[21] The relative configuration within **36** was proven by X-ray crystallography (Figure 4),[22] with the relative configuration within **25**, **29**, **33**, **37**, and **41** also assigned by NOESY analysis.

In conclusion, we have shown that isothiourea DHPB **15** promotes the efficient *C*-acylation of silyl ketene acetals with high levels of stereoselectivity (up to 99/1 dr) using a range of anhydrides or benzoyl fluoride as the acylating agents. Ongoing studies within this laboratory are directed toward the demonstration of catalytic asymmetric versions of related reaction protocols and developing alternative uses of isothioureas in asymmetric catalysis.

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Supporting Information Available: Experimental procedures plus spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For diastereoselective *C*-acylations using chiral auxiliaries, see: Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156. Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015–6016.

(16) See Supporting Information for full details.

(17) The use of benzoic anhydride in this protocol gave excellent conversion to **20** in >98/2 dr, but **20** proved difficult to purify to homogeneity in this case because of co-elution with excess benzoic anhydride.

(18) For select examples of highly diastereoselective alkylations of butyrolactones that proceed *anti* to a C(5)-stereodirecting group (typical dr >95/5), see: Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *Chem. Lett.* **1981**, 1621–1624. Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094–4098.

(19) While this simplistic model accounts for the observed sense of stereoselectivity, the lowest energy conformations of neither the presumed enolate nor the *C*-acyl isothiouronium intermediate, or the transition state for the reaction, have yet been calculated computationally. Efforts towards this goal are currently under further investigation.

(20) Reactions were typically performed with 0.5 mmol of the requisite silyl ketene acetal. For one example, we have demonstrated that scaling to 5 mmol furnishes **25** in similar yield and dr (87% yield, 98/2 dr).

(21) Benzoyl fluoride or isobutyric anhydride with DHPB gave only low conversion to the corresponding *C*-acyl products.

(22) Crystallographic data for **36** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 772460.