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Thiazolium-Catalyzed Additions of Acylsilanes: A General Strategy for Acyl Anion Addition Reactions

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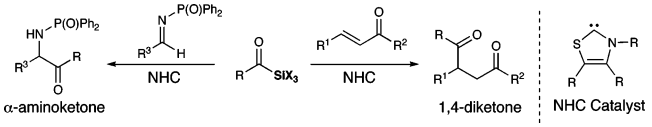

A strategy utilizing N-heterocyclic carbenes (NHCs) derived from thiazolium salts has been developed for the generation of carbonyl anions from acylsilanes. Synthetically useful 1,4-diketones and *N*-phosphinoyl-α-aminoketones have been prepared in good to excellent yields via NHC-catalyzed additions of acylsilanes to the corresponding α,*β*-unsaturated systems and *N*-phosphinoylimines. These organocatalytic reactions are air- and water-tolerant methods to execute robust carbonyl anion addition reactions. Additionally, polysubstituted aromatic furans and pyrroles have been efficiently synthesized in a one-pot process using this carbonyl anion methodology. The addition of alcohols to the reaction renders the process catalytic in thiazolium salt. In an effort to synthesize a potential intermediate along the proposed reaction pathway, silylated thiazolium carbinols have been identified to provide good yields of carbonyl anion addition products when subjected to the standard reaction conditions in the presence of suitable electrophiles.

Introduction

N-Heterocyclic carbenes (NHCs) have been shown to be highly useful compounds able to participate in a number of diverse reactions.[2−9] Because of their unusual electronic characteristics, they are unique molecular architectures for the development of new organometallic processes,[7,10−13] catalysts in organocatalytic reactions,[7,8,14−27] and reagents in multicomponent coupling reactions.[28−31] A valuable synthetic tactic that NHCs are capable of catalyzing is the polarity reversal, or *Umpolung*,[32] of carbonyl-containing compounds. Umpolung strategies are highly useful methods to form carbon−carbon bonds through unconventional modes of reactivity. The polarity reversal of carbonyl units generates carbonyl or acyl anions, a

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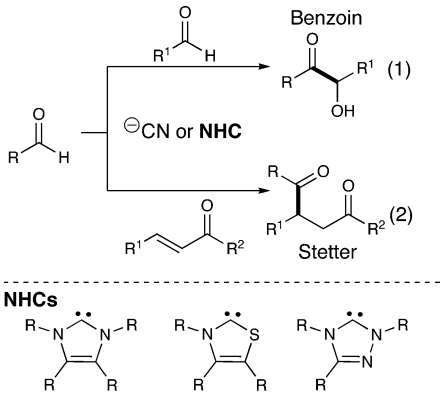
SCHEME 1. Catalytic Acyl Anion Addition Reactions with Aldehydes Employed as Acyl Anion Precursors

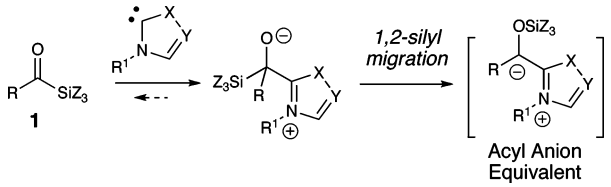


useful class of reactive intermediates. Many important biological processes utilize carbonyl anions generated from the corresponding α-keto acids via an NHC derived from thiamine pyrophosphate, a cofactor of vitamin B_1.

Two established catalytic acyl anion addition reactions are the benzoin condensation[33−36] (1,2-addition of a carbonyl anion to an aldehyde, Scheme 1, eq 1) and the Stetter reaction[37−42] (1,4-addition of a carbonyl anion to an α,β-unsaturated system, eq 2). In these processes, a catalyst, such as cyanide or an NHC, is used to generate an acyl anion equivalent from an aldehyde. Unfortunately, because of the highly reactive nature of aldehydes, a significant amount of self-condensation side products are often formed when they are employed as acyl anion precursors. The intrinsic reactivity of the starting aldehyde is advantageous when generating a carbonyl anion species via addition of an NHC, but this aspect is limiting in that multiple products are observed when electrophiles that are less reactive than aldehydes are employed.

Acylsilanes[43−48] are useful molecules that have been utilized as unconventional acyl anion precursors. Acylsilanes are more sterically congested than aldehydes because of the substitution on silicon, and this attenuated reactivity precludes side reactions associated with additions to carbonyl groups. The standard method to convert acylsilanes into carbonyl anions typically involves the addition of charged nucleophilic species, such as

SCHEME 2. N-Heterocyclic Carbene-Catalyzed Generation of Acyl Anions



fluoride or cyanide anions. In 1981, the Heathcock laboratory reported the use of fluoride (KF, tetrabutylammonium fluoride) to promote alkylation of the carbonyl carbon of acylsilanes with various alkyl halides.[49] These findings were followed by disclosures from Degl'innocenti and co-workers showing the conjugate additions of acylsilanes to enones catalyzed by either fluoride or cyanide.[50] More recently, Johnson has reported asymmetric cross-benzoin reactions of acylsilanes and aldehydes catalyzed by cyanide or metallophosphite species.[36] These nucleophilic phosphorus compounds have also been shown to promote conjugate additions of acylsilanes to unsaturated carbonyl compounds.[51]

Beginning in 2002, our laboratory has focused on developing strategies to catalyze carbonyl anion addition reactions under more neutral reaction conditions than those previously reported. On the basis of the pioneering work by Heathcock and Degl'innocenti, we chose acylsilanes to investigate as a unique carbonyl anion precursor. It is well established that NHC catalysis can be used to generate acyl anion equivalents from aldehydes,[8,9,15,35] and we envisioned applying this same approach to acylsilanes. At the onset of our investigations, it was reasonable to propose that an NHC would undergo nucleophilic addition to an acylsilane (**1**) and promote a 1,2-silyl group shift (Brook rearrangement)[52,53] from carbon to oxygen, thus rendering the carbonyl carbon nucleophilic (Scheme 2). However, when compared to smaller nucleophiles such as fluoride and cyanide anions, it was unclear whether a larger five-membered heterocycle such as a thiazolium would add to the carbonyl carbon of an acylsilane. Indeed, heteroazolium carbenes/zwitterions had not been used to promote Brook rearrangements of acylsilanes prior to our findings. As mentioned, these overall neutral carbenes/zwitterions have found utility as organocatalysts in a variety of reactions, can be generated in situ from stable precursors, tolerate air and moisture, and are generally nontoxic.

In preliminary communications, we have reported the addition of acylsilanes to α,β-unsaturated systems and imines to generate the corresponding 1,4-diketones[54] and α-aminoketones[55] using

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SCHEME 3. Acylsilane Addition Reactions Catalyzed by NHCs

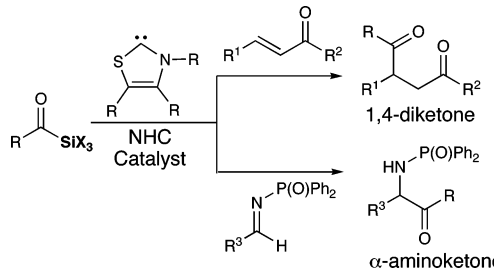
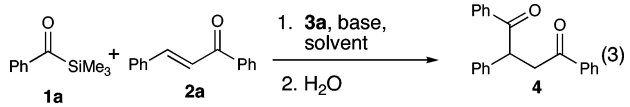


TABLE 1. Optimization of Acylsilane Additions to Chalcone with Stoichiometric Thiazolium Salt[a]



entry	base	solvent	yield (%)[b]
1	DBU	THF	71
2	NEt_3	THF	40
3	KO^{t}Bu	THF	0
4	DBU	CH_2Cl_2	39
5	DBU	$PhCH_3$	0

[a] Reaction performed at 0.8 M for 12−24 h at reflux in the solvent indicated. [b] Isolated yield after chromatographic purification.

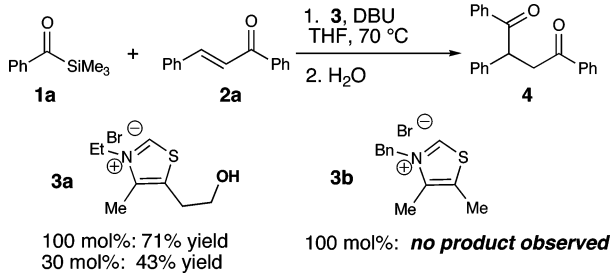
NHC catalysts derived from commercially available thiazolium salts (Scheme 3). This full account describes in detail the development of our NHC-catalyzed acylsilane addition reactions, including an examination of the catalyst structure and mechanistic studies.

Results and Discussion

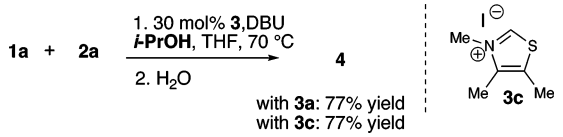
Development of a Successful NHC Catalyst System. Our investigation of NHC-catalyzed acyl anion additions began with a survey of reaction conditions to carry out 1,4-additions of acylsilanes to chalcone. Our choice of pursuing the synthesis of 1,4-dicarbonyl compounds via a carbonyl anion addition was driven by the utility of these molecules in organic synthesis. After significant experimentation, we discovered that a stoichiometric amount of thiazolium salt **3a** and DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) successfully promotes the addition of benzoyltrimethylsilane **1a** to chalcone to produce 1,4-dicarbonyl **4** in a good yield after 12 h of reflux in THF (71%, Table 1, entry 1). With the desired bond-forming process achieved, a brief survey of bases and solvents indicated that DBU and THF were optimal. Methylene chloride provided only a 39% yield product, most likely because of the low reaction temperature (entry 4). The use of toluene as a solvent resulted in a heterogeneous mixture that afforded no product formation (entry 5).

After successful formation of **4** in the stoichiometric process, we focused on developing a catalytic acylsilane addition reaction. On the basis of our knowledge of the Stetter reaction, we suspected that the process should be catalytic in thiazolium salt; however, when the amount of **3a** was reduced from 1 equiv to 30 mol %, only a 43% yield of the product was isolated

SCHEME 4. Acylsilane Additions to Chalcone with Catalytic Thiazolium Salt



SCHEME 5. Catalytic Sila-Stetter Reaction with Exogenous Alcohol



(Scheme 4). A more surprising result was obtained when no product was observed with a stoichiometric amount of catalyst **3b**.

A comparison of catalysts **3a** and **3b** reveals that the free alcohol (an artifact of the conversion of thiamine into structures such as **3a**) may be the cause for the difference in reactivity. To explore whether a free alcohol was necessary for the reaction, 4 equiv of 2-propanol was added to an acylsilane addition reaction containing 30 mol % of **3a** (Scheme 5). We were pleased to find that the straightforward addition of an exogenous alcohol improved the yield of **4** to 77% with only 30 mol % of **3a**. Further confirmation of the importance of an alcohol additive was observed when thiazolium **3c** was employed with 4 equiv of 2-propanol: these reaction conditions provided the same yield as with **3a**. These results show the counterion has a minimal effect on the outcome of the acylation reactions.

A key variable we were interested in examining was the structure of the heteroazolium catalyst. The reactivity of an NHC can significantly be affected by steric and electronic properties; therefore, an examination of potential catalysts was carried out to determine the best NHC to effect the desired conjugate addition. To our surprise, NHCs derived from imidazolium and triazolium compounds fail to produce significant amounts of the desired product **4** (Table 2, eq 4). Surprisingly, the catalyst derived from benzothiazolium **3d** does *not* provide any of the desired product, thereby underscoring the subtle electronic effects that control the interaction of the heteroazolium-derived carbene with the acylsilane as well as the carbon−carbon bond forming process. Additionally, no decomposition of the chalcone or acylsilane is observed with **3d**. There is no product formation with the sterically hindered catalyst resulting from imidazolium salt **3e**, although some acylsilane is consumed. Interestingly, benzaldehyde is the only product resulting from the reaction catalyzed by **3e** and no benzoin products were observed by gas chromatography. The benzimidazolium-derived catalyst (**3f**) affords nearly complete conversion of the acylsilane, but only a 5% yield of 1,4-diketone **4** is observed. Triazolium-derived catalysts **3g** and **3h** had similar results, with little product formation and little recovered acylsilane. These observations emphasize how slight perturbations in the heteroazolium core and nitrogen substitution can cause drastic differences in reactivity.

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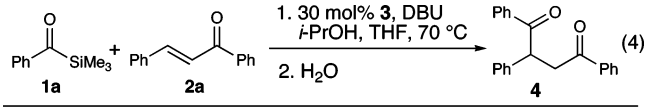
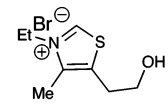
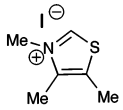
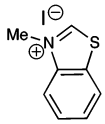
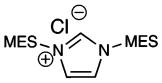
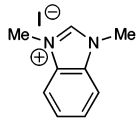
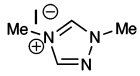
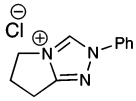
TABLE 2. Examination of Catalyst Structure[a]

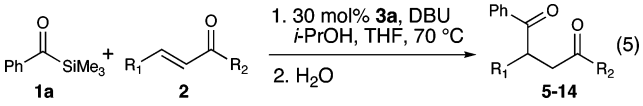


entry	catalyst		1a conversion	2 conversion	yield[b]
1		**3a**	100%	100%	77%
2		**3c**	100%	100%	77%[c]
3		**3d**	0%	0%	0%
4[d]		**3e**	50%	31%	0%
5		**3f**	74%	9%	5%
6		**3g**	100%	53%	7%
7		**3h**	93%	27%	0%

[a] Reactions performed at 0.5 M for 24 h. [b] Yields and conversions obtained by GC unless otherwise noted. [c] Isolated yield after purification. [d] Mes = Mesityl.

Investigation of Acylsilane Additions to α,β-Unsaturated Electrophiles. With an operative catalytic process identified, we proceeded to examine the scope of the addition reaction of various acylsilanes to α,β-unsaturated systems. After our initial success with chalcone (**2a**), we screened numerous unsaturated amides and esters as electrophiles with no success. A current requirement of our acylsilane conjugate additions is that the electrophile needs to be an α,β-unsaturated ketone or a highly reactive ester. Utilizing an unsaturated acyl pyrrole as the electrophile produced a complex mixture of compounds with no desired carbonyl anion products. Additionally, no desired product was observed when a cyclic ester and amide, maleic anhydride, and *N*-methyl maleimide were examined. Additions to alkylidene malonates were met with limited success as low conversions prevented high yields of product from being isolated. Our attempts to add to nitroalkenes failed because the starting materials decomposed under these reaction conditions. Our investigations of the chalcone substrate scope began with an examination of various substituted derivatives (Table 3, eq 5). The addition reaction can tolerate both electron-donating and electron-withdrawing substituents on either aryl group, delivering good to high yields of product in all cases (66−82%, entries 1−9). Even a free hydroxyl group provides the desired 1,4-diketone **14**, albeit in a slightly reduced yield (50%, entry 10). Because 2-propanol is a key constituent in the reactions,

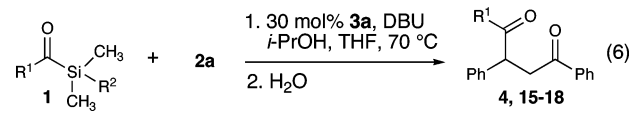
TABLE 3. Catalytic Sila-Stetter Reaction with Acylsilane 1a and β-Aryl Unsaturated Phenyl Ketones[a]



entry	R^1	R^2	yield (%)[b]	product
1	Ph	4-ClPh	82	**5**
2	Ph	4-OMePh	80	**6**
3	1-naphth	Ph	72	**7**
4	4-BrPh	Ph	66	**8**
5	4-ClPh	Ph	74	**9**
6	2-ClPh	Ph	68	**10**
7	4-MePh	Ph	84	**11**
8	3-OMePh	Ph	75	**12**
9	4-OMePh	Ph	77	**13**
10	4-HOPh	Ph	50[c]	**14**

[a] Reaction performed at 0.8 M for 12−24 h. [b] Isolated yield after chromatographic purification. [c] Based on 70% conversion.

TABLE 4. Catalytic Sila-Stetter Reaction with Acylsilane 1a and β-Aryl Unsaturated Phenyl Ketones[a]



entry	acylsilane	R^1	R^2	yield (%)[b]	product
1	**1a**	Ph	CH_3	77	**4**
2	**1b**	4-ClPh	CH_3	82	**15**
3	**1c**	4-CH_3Ph	CH_3	70	**16**
4	**1d**	Ph	Ph	61	**4**
5	**1e**	CH_3	Ph	70	**17**
6	**1f**	cyclohexyl	Ph	63	**18**

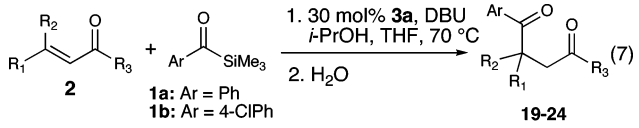
[a] Reaction performed at 0.8 M for 12−24 h. [b] Isolated yield after chromatographic purification.

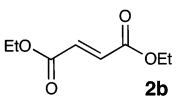
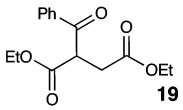
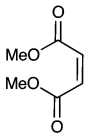
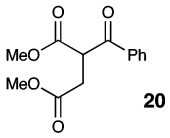
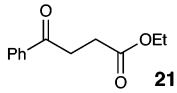
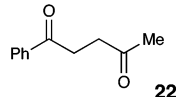
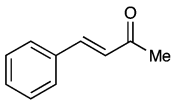
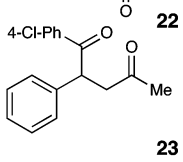
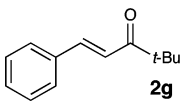
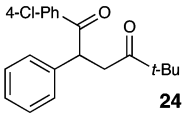
there are no stringent precautions to exclude moisture in any of these reactions.

The influence of the acylsilane structure on the reaction was also examined (Table 4, eq 6). Because the addition of a thiazolium-derived carbene/zwitterion is an important step in the overall process, the substitution of the silyl group should influence the accessibility to the carbonyl carbon atom. Accordingly, both alkyl and substituted aryl acylsilanes were investigated as acyl anion precursors. Acylsilane **1b** containing an electron-withdrawing substituent in the para position provided the best results, generating **15** in 82% yield (Table 4, entry 2). Interestingly, **1b** is the most reactive acyl anion precursor we have surveyed. This may be due to the ability of this analogue to offer additional stabilization to the carbonyl anion equivalent that is generated in the reaction. Acylsilanes with alkyl groups at R_1 (**1e** and **1f**) are successful substrates and generate 1,4-diketone products **17** and **18** in good yields (entries 5 and 6). These entries indicate that the reaction can accommodate acylsilanes with enolizable protons. Additionally, dimethylphenyl acylsilane **1d** proved to be a suitable acyl anion precursor yielding 61% of **4** (entry 4).

The scope of the sila-Stetter reaction was further examined by employing various classes of α,β-unsaturated carbonyl electrophiles (Table 5, eq 7). Even with multiple nucleophilic species in solution (e.g., DBU, 2-propanol, thiazolium carbene/zwitterion), a surprising number of highly reactive conjugate acceptors that are prone to polymerization provide moderate yields of 1,4-dicarbonyl products. Diethyl fumarate and dimethyl

TABLE 5. Acylsilane Additions to β,β-Unsaturated Esters and Ketones[a]



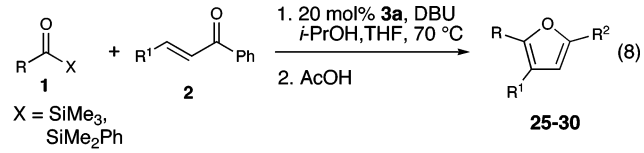
entry	Ar	2	product	yield[b]
1	1a	 2b	 19	65%
2	1a	 2c	 20	72%
3	1a	 2d	 21	72%
4	1a	 2e	 22	75%
5	1b	 2f	 23	63%[c]
6	1b	 2g	 24	48%[d]

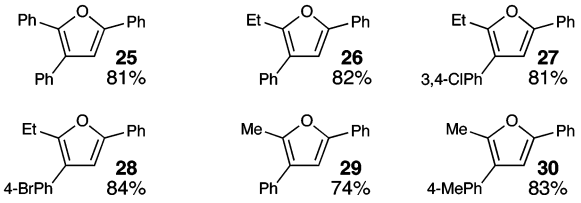
[a] Reactions performed at 0.8 M for 12−24h. [b] Isolated yield after chromatographic purification. [c] 64% conversion. [d] 59% conversion.

malonate are competent substrates generating the corresponding products **19** and **20** in good yield (entries 1 and 2). Highly reactive substrates lacking substitution in the β-position such as ethyl acrylate and methyl vinyl ketone undergo these nucleophilic acylation reactions to generate **21** and **22** in 72% and 75% yields (entries 3 and 4). Finally, additions to alkyl chalcone derivatives **2f** and **2g** produce the desired 1,4-diketones in moderate yields (entries 5 and 6). In this system, alkyl chalcones are less reactive than aryl chalcones and the lower yields are a result of the reactions not going to completion under numerous conditions surveyed. In an effort to aid in the conversion of the alkyl chalcones, acylsilane **1b** containing the *p*-Cl substituent was employed because it is the most reactive acyl anion precursor that we have examined.

One-Pot Synthesis of Furans and Pyrroles. With a robust and efficient preparation of 1,4-dicarbonyl compounds developed, we became interested in applying this new Umpolung methodology to a one-flask synthesis of highly substituted heterocycles. Initially, our efforts were directed toward the synthesis of furans because these important heterocycles are easily accessible from 1,4-diketones and are found in natural products, pharmaceuticals, and materials.[56] Although there are many strategies available to synthesize these valuable compounds,[57,58] we envisioned that our addition reaction could be the first step in a direct, one-flask process to access polyaromatic furans without the need for a transition-metal catalyst. Thus, the 1,4-dicarbonyl compounds synthesized by the thiazolium-catalyzed conjugate addition of acylsilanes could be directly converted to furans in a one-pot process upon simple addition of an acid.

TABLE 6. Examples of Furans Prepared in a One-Flask Synthesis[a,b]





[a] All reactions performed at 1.0 M for 24 h. See Supporting Information for details. [b] Isolated yields after chromatographic purification.

We were pleased to find that straightforward addition of acetic acid to the reaction after 100% conversion of the conjugate acceptor followed by stirring at reflux for 8 h yielded the desired furan product **25** (Table 6, eq 8). In this process, both alkyl and aryl acylsilanes successfully participate in the one-pot reaction with a variety of chalcone derivatives, providing excellent yields of highly substituted furans (74−84%). Notably, these yields are for a two-step process yielding greater than 90% per step.

Encouraged by the efficiency of our simple furan synthesis, this one-flask strategy has been applied to the synthesis of 2,3,5-trisubstituted pyrroles.[59] The addition of a primary amine to a 1,4-dicarbonyl compound in the presence of acid accesses pyrroles in good yield and is known as the Paal−Knorr cyclization.[60−62] The combination of our conjugate addition with a Paal−Knorr reaction in a single flask would constitute the multicomponent assembly of polyaromatic pyrroles. Rapid access to various substituted pyrroles is a continuing goal in organic chemistry because these heterocycles are important motifs in natural products,[63−66] therapeutic compounds,[67,68] and materials.[69−71] Accordingly, new synthetic approaches to access

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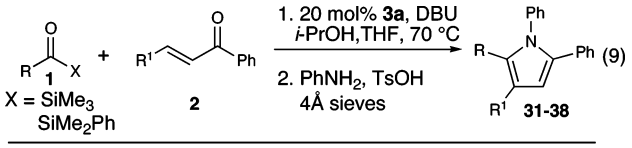
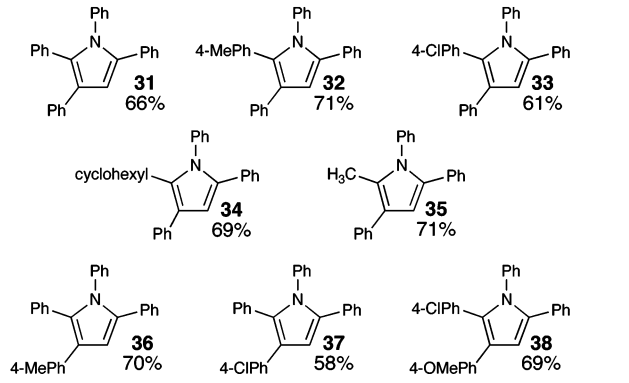
TABLE 7. Select Examples of Pyrroles Synthesized in a One-Pot Sila-Stetter Process[a,b]





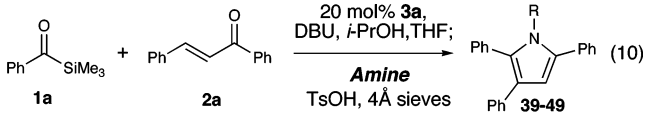
[a] All reactions performed at 0.8 M for 16 h. See Supporting Information for details. [b] Isolated yields after chromatographic purification.

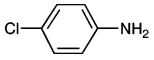
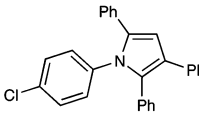
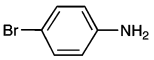
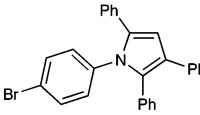
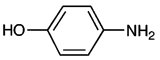
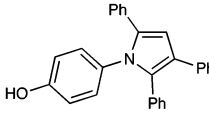
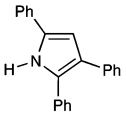
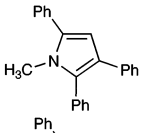
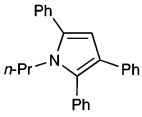
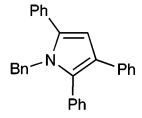
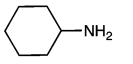
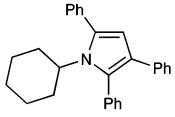
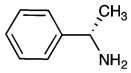
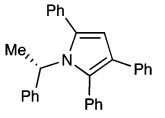
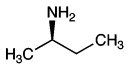
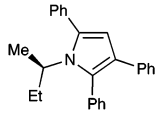
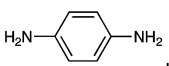
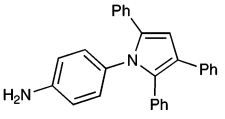
pyrroles continue to be an area of intense research.[72−75] Our multicomponent approach is similar to the furan synthesis above in efficiency and avoidance of expensive and/or toxic transition-metal catalysts.

To optimize this conjugate addition/Paal−Knorr sequence, various acids were added directly along with aniline to a thiazolium-catalyzed reaction between **1** and **2** after 100% conversion of **2**. With *p*-toluenesulfonic acid (TsOH) after 8 h at reflux, moderate to good yields of the pyrroles can be isolated. In this manner, a wide array of highly substituted pyrroles can be readily prepared (Table 7, eq 9). The reaction is tolerant of various substituted chalcones, including both electron-donating and electron-withdrawing substituents. Additionally, pyrroles were easily generated from an assortment of alkyl and aryl acylsilanes in high yield. To gain an additional element of diversity, the amine was investigated (Table 8, eq 10). Substituted anilines proved to be suitable substrates, as both electron-donating and -withdrawing analogues generated the desired pyrroles in high yield (entries 1−3). Both straight chain and branched alkylamines successfully participate in the cyclization reactions to yield the desired products in 63−82% yields (entries 5−8). Chiral pyrroles **47** and **48** were generated in good yield from optically active amines (entries 9 and 10).

Although this multihour process affords good yields of pyrroles, we felt that a more efficient means of heating could reduce the time required and thus improve the overall process. The use of microwave heating[76−78] significantly reduces the overall time for this two-step, single-flask process (Scheme 6). The first heating cycle for 15 min at 160 °C combines **1a** and α,β-unsaturated ketone **2** in the presence of 20 mol % of **3a**, 30 mol % of DBU, and 4 equiv of 2-propanol. This sequence

TABLE 8. Survey of Amines for Pyrrole Synthesis[a]



entry	Amine	pyrrole		yield (%)[b]
1			**39**	57
2			**40**	71
3			**41**	61
4	$H_4N{\cdot}O_2CCH_3$		**42**	62
5	CH_3NH_2		**43**	70
6	$CH_3(CH)_2NH_2$		**44**	82
7	$PhCH_2NH_2$		**45**	65
8			**46**	63
9			**47**	54
10			**48**	56
11			**49**	70

[a] Reaction conditions: 20 mol % of **4** and 30 mol % of DBU, 4 equiv of *i*-PrOH; 0.8 M at 70 °C for 8 h. Amine, TsOH, and 4 Å sieves were then added for an additional 8 h. [b] Isolated yield after purification.

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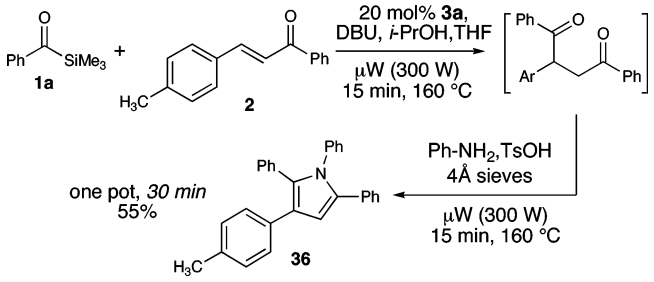
(78) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

SCHEME 6. One-Pot Pyrrole Synthesis in the Microwave



is followed by the addition of aniline and TsOH, and a second 15 min heating cycle at 160 °C smoothly affords the desired pyrrole (**36**) in 55% yield in only 30 min. This streamlined approach generates the target heterocycle in 3% of the time required using conventional heating (30 min vs 16 h).

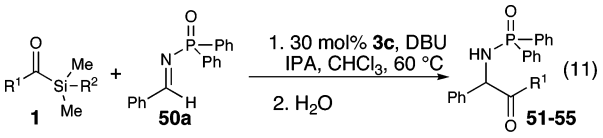
Investigation of Acylsilane Additions to Imines. The successful conjugate additions of acylsilanes confirmed that NHCs could promote carbonyl anion reactions. After exploring different unsaturated ketones as electrophiles in these 1,4-additions, we turned our attention toward developing the related 1,2-addition manifold. Acylsilane additions to activated imines would enable the direct preparation of α-aminoketone products, valuable compounds in synthetic and medicinal chemistry.[79−81] Although powerful methods exist to generate α-amino acids from imines, such as the Strecker reaction,[82−84] the options to directly synthesize protected α-aminoketones are limited.

The optimal conditions were established using a similar catalyst system that was developed for the 1,4-addition reactions. Chloroform and 2-propanol combined with the carbene derived from thiazolium salt **3c** and DBU provided an excellent yield of α-aminoketone **51** (93%, Table 9, entry 1). It is important to note that the phosphinoyl protecting group is crucial for success in these reactions. The other imines surveyed (*N*-Bz, *N*-sulfinyl, *N*-sulfonyl) were unsuccessful in this process. For these nucleophile-catalyzed reactions, a careful balancing of reactivity must be present: the ultimate electrophile (conjugate acceptor or imine) cannot interact irreversibly with the nucleophilic catalysts. The unique characteristics of *N*-phosphinoylimines[85] in these acylsilane additions vs other imines underscore this point.

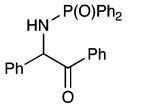
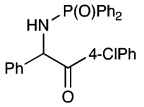
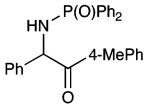
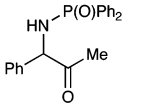
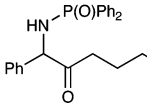
With the optimal conditions now identified, we examined the scope of this 1,2-addition reaction with regard to the acylsilane structure and imine substitution. First, the effect of the acylsilane structure on the reaction was examined. In a vein similar to the previous conjugate additions, the imine process can accommodate either alkyl or aryl acylsilanes, producing high yields of product in all cases (Table 9, eq 11). An acylsilane with a protected alcohol is a competent acyl anion precursor in the reactions (entry 5).

Various aromatic substituted *N*-phosphinoylimines were also examined as electrophiles in the acylsilane addition reactions

TABLE 9. Effect of Acylsilane Structure on Addition to Imines[a]



(11)

entry	R^1	R^2	product		yield[b]
1	Ph	Me		**51**	93%
2	4-ClPh	Me		**52**	90%
3	4-MePh	Me		**53**	81%
4	Me	Ph		**54**	87%
5	$(CH_2)_3OBn$	Ph		**55**	63%

[a] All reactions performed at 0.5 M for 12−24 h. See Supporting Information for details. [b] Isolated yields after silica gel chromatography.

(Table 10, eq 12). Imines containing electron-withdrawing substituents on the aryl ring, such as 4-Cl and 2-Cl, are suitable substrates generating high yields of the corresponding α-aminoketone products (entries 1 and 4). The imine derived from *para*-anisaldehyde produced an excellent yield of **58** (86%, entry 3). The reaction can also successfully incorporate heterocycles, such as thiophene, into the final product in high yield (80%, entry 5). The use of *N*-phosphinoylimines derived from alkyl-substituted aldehydes did not generate 1,2-addition products because the presence of an enolizable proton allows for facile conversion to the more stable enamide. In an attempt to avoid this problem by generating only small concentrations of reactive imine during the reaction, Charette's method using sulfinic acid adducts of imines was employed.[86] Unfortunately, no desired products were observed using the imine precursors.

Reaction Pathway. With the successful development of 1,2- and 1,4-acylsilane addition reactions, we became interested in a deeper understanding of the mechanism of these NHC-catalyzed processes. We have advanced a plausible reaction pathway based on the mechanism proposed for the benzoin condensation (Scheme 7).[35,87−94] The deprotonation of the

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(84) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634−5635.
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(87) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124−5131.
(88) Chen, Y. T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 7714−7722.
(89) Chen, Y. T.; Jordan, F. *J. Org. Chem.* **1991**, *56*, 5029−5038.
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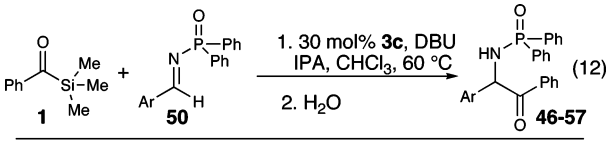
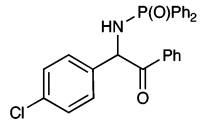
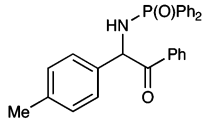
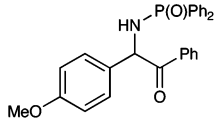
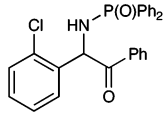
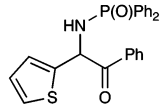
(91) Jordan, F.; Kudzin, Z. H.; Rios, C. B. *J. Am. Chem. Soc.* **1987**, *109*, 4415−4416.
(92) Rios, C. B.; Chung, A.; Jordan, F. *Biochemistry* **1988**, *27*, 3107−3107.
(93) Jordan, F. *Nat. Prod. Rep.* **2003**, *20*, 184−201.
(94) Kluger, R. *Chem. Rev.* **1987**, *87*, 863−876.

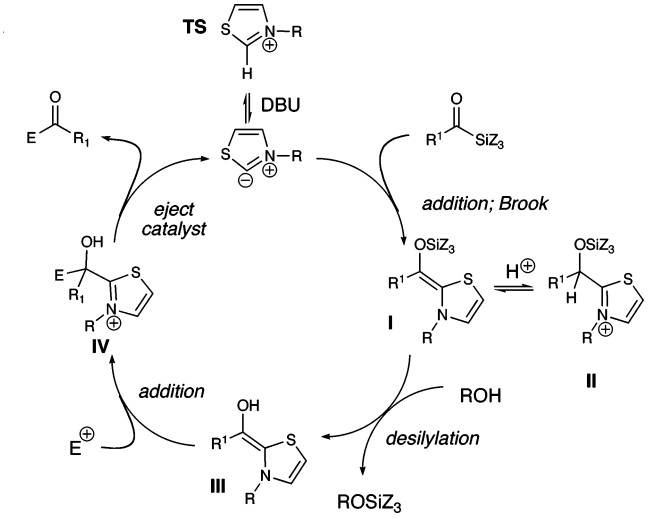
TABLE 10. Examination of Acylsilane Additions to Phosphoyl Imines[a]



entry	Ar	product		yield[b]
1	4-ClPh		**56**	85%
2	4-MePh		**57**	94%
3	4-OMePh		**58**	86%
4	2-ClPh		**59**	77%
5	2-thiophene		**60**	80%

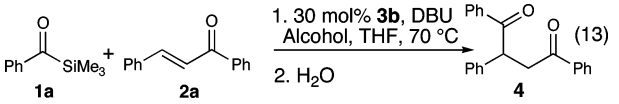
[a] All reactions performed at 0.5 M for 12−24 h. See Supporting Information for details. [b] Isolated yields after silica gel chromatography.

SCHEME 7. Proposed Reaction Pathway



thiazolium salt (**TS**) yields the nucleophilic carbene. The addition of the NHC to an acylsilane generates a tetrahedral intermediate which undergoes a 1,2-silyl group migration from carbon to oxygen (Brook rearrangement). This thermodynamically driven migration produces acyl anion equivalent **I** (after electronic reorganization). The carbon with the silyloxy group appended is now nucleophilic by virtue of the connecting enamine and is most likely in equilibrium with **II** when in the presence of an available proton. All attempts to observe and/or isolate compounds such as **I** have been fruitless (vide infra). Although the reactive characteristics of a species such as the *O*-silyl heterocycle **I** remain uncertain, the geminal substitution on the nucleophilic carbon **I** renders a nucleophilic addition at this point in the catalytic cycle energetically unfavorable. Instead, it is plausible that a desilylation of **I** occurs in the presence of DBU and an alcohol (such as 2-propanol) to yield **III**, a less sterically hindered acyl anion equivalent able to undergo addition reactions with greater facility. Enol/enamine structures similar to **III** were first invoked as the carbonyl anion species in the seminal work on the mechanism of the benzoin reaction by Breslow and thus were termed "Breslow intermediates". The nucleophilic addition of **III** to the electrophile forms the key carbon−carbon bond which is followed by collapse of the carbonyl to regenerate the thiazolium catalyst and produce the acylated product.

TABLE 11. Effect of Alcohol on Acylsilane Additions to Chalcone[a]



entry	alcohol	pK_a (DMSO)	yield (%)[b]
1	EtOH	28	56
2	*i*-PrOH	29	85
3	*t*-BuOH	29	99
4	$(CF_3)_2CH_2OH$	18	70
5	phenol	18	81

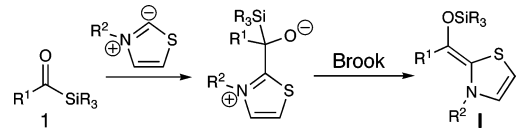
[a] All reactions performed at 0.8 M for 24 h. [b] Yields obtained by GC.

To gain an improved understanding of the addition reactions described above, we investigated the role of the alcohol in the reaction and carried out a synthesis and investigation of potential intermediate **II**. We were initially puzzled by the observation that thiazolium salts such as **3b** lacking a hydroxyl group afforded *no* product without 2-propanol. However, after determining that a full equivalent of a hydroxyl group must be present on the thiazolium or as an additive for the reaction to proceed to 100% conversion, we concluded that the alcohol is involved in the generation of the carbonyl anion and not catalyst turnover. 2-Propanol had been the alcohol of choice; however, a more thorough investigation revealed that the alcohol structure had only a moderate effect on the yield (Table 11, eq 13). Interestingly, more sterically hindered alcohols such as *tert*-butyl alcohol are slightly better additives, providing a quantitative yield of 1,4-diketone **4** (entry 3). Surprisingly, the acidity of the alcohol additive has a minimal impact on the overall process. On the basis of experiments monitored by GC, the alcohol additive is the ultimate silyl acceptor. These data support the hypothesis that the alcohol additive promotes desilylation of **I**: enolsilanes are known to be mild silylating agents,[95−97] whereas silyl ethers (such as O-silylated versions of **IV**) are less prone to donate a silyl group. However, this observation does not confirm that intermediates such as **I** undergo desilylation because silyl group transfer after addition of **I** to an electrophile cannot be ruled out at this time. The elusive nature of compounds such as **I** (vide infra) has made the delineation of the exact role of the alcohol additive difficult.

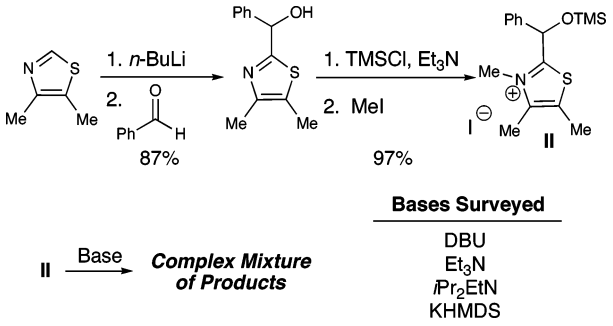
Synthesis and Examination of a Potential Reaction Intermediate. To further probe the mechanism of these acylsilane

(95) Mcwilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378−8379.
(96) Veysoglu, T.; Mitscher, L. A. *Tetrahedron Lett.* **1981**, *22*, 1303−1306.
(97) Veysoglu, T.; Mitscher, L. A. *Tetrahedron Lett.* **1981**, *22*, 1299−1302.

SCHEME 8. Proposed First Step in Acylsilane Additions



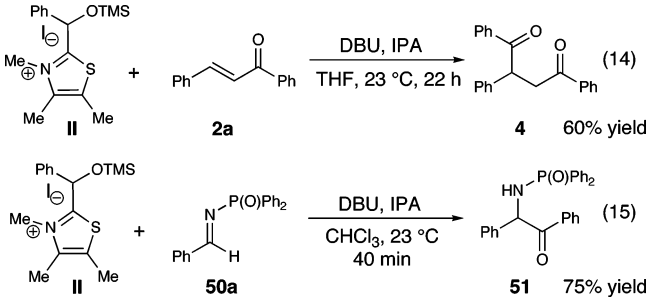
SCHEME 9. Attempted Synthesis of Proposed Intermediate I



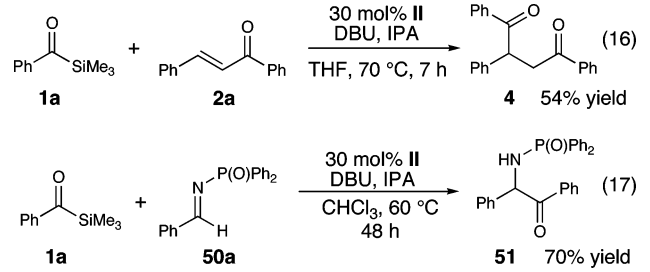
additions, we attempted to synthesize a silylated Breslow intermediate with a structure similar to **I** in our proposed reaction pathway. Access to compounds such as **I** would allow us to assess their ability to undergo addition reactions with or without an alcohol present. This species is invoked in our reaction pathway and could be produced in a manner very similar to the first steps in the proposed catalytic cycles of the benzoin condensation and Stetter reaction.[35,87] In these Umpolung processes, the addition of a thiazolium-derived catalyst to the aldehyde followed by a 1,2-proton shift to generate the acyl anion equivalent occurs. We suspected that a similar sequence was occurring in our addition reactions in which the interaction of a thiazolium carbene/zwitterion with acylsilane generates intermediate **I** (Scheme 8). To probe whether **I** was involved as an intermediate in the reaction, an independent synthesis was required. This was attempted by first lithiating 4,5-dimethylthiazole at the 2-position using *n*-butyllithium and then reacting with an aldehyde (Scheme 9). The resulting carbinol was purified by simple recrystallization (ethyl acetate/hexanes) and then protected with a trimethylsilyl group (TMS) in the presence of triethylamine. Finally, the thiazolium salt was prepared by straightforward alkylation with neat iodomethane at 80 °C. Confirmation of the synthesis of desired intermediate **II** was obtained by ^{1}H and ^{13}C NMR spectroscopy. We anticipated that intermediate **I** could be generated by deprotonation of the protected thiazolium carbinol **II**. Unfortunately, upon addition of base (DBU, Et_3N, iPr_2EtN, KHMDS) to the thiazolium carbinol, only decomposition was observed by TLC or ^{1}H NMR. However, because of the nature of the acylsilane addition reactions, we speculated thiazolium salt **II** may be an intermediate in the process. As depicted in Scheme 7, this thiazolium salt (**II**) could be in equilibrium with **I** and this pathway would provide a different entry into the catalytic cycle.

To probe this possibility, thiazolium carbinol **II** was employed in two separate reactions, with chalcone (**2a**) and *N*-phosphinoylimine **50a** using previously established reaction conditions (Scheme 10, eqs 14 and 15). In both cases, *the desired product was observed in good yield lending support to the hypothesis that **II** is an intermediate in these addition reactions.* Interestingly, the reactions readily occurred in the absence of heat. In a second set of experiments, the thiazolium carbinol was added to the reaction in place of the NHC precursor (Scheme 11, eqs 16 and 17). Gratifyingly, both reactions generated the desired

SCHEME 10. Examination of II in Addition Reactions



SCHEME 11. Examination of II in Addition Reactions



products in good yield providing additional evidence for intermediate **II** participating in the reaction.

Conclusions. A new strategy has been developed to generate carbonyl anion equivalents from acylsilanes. We have demonstrated that in the presence of an alcohol additive neutral NHCs, generated in situ from commercially available thiazolium salts, successfully catalyze the addition of acylsilanes to α,β-unsaturated systems and *N*-phosphinoylimines to generate the corresponding 1,4-diketones and α-aminoketones in good to excellent yields. Furthermore, highly substituted furans and pyrroles can be synthesized via efficient one-pot sila-Stetter/cyclization sequences. Benzoin side-product formation is not observed in these processes, strongly indicating that the acylsilane does not self-condense under the reaction conditions. To probe the mechanism of these new bond-forming reactions, a proposed reaction intermediate was independently synthesized and examined under a variety of conditions. The expected products are observed in all cases when this potential intermediate is subjected to a variety of reaction conditions providing substantial evidence for the proposed reaction pathway. Finally, an investigation of the alcohol additive revealed that it is necessary for successful generation of carbonyl anions with acylsilanes and thiazolium salts and also plays the role of the final silyl group acceptor. Continued investigation into the full potential of this NHC/acylsilane combination is ongoing in our laboratory, and the development of related NHC-catalyzed Umpolung reactions is currently underway.

Experimental Section

General Procedure for Thiazolium-Catalyzed Acylsilane Additions to α,β-Unsaturated Systems. A screw-capped test tube was charged with the thiazolium salt (30 mg, 0.119 mmol) and placed under a positive pressure of nitrogen. Benzoyltrimethylsilane (140 mg, 0.768 mmol) in THF (0.25 mL) was added by syringe to the test tube followed by the addition of DBU (17 μL, 0.119 mmol). The reaction mixture was heated to 70 °C after which the chalcone (0.384 mmol) in THF (0.25 mL) was added by syringe followed by the addition of 2-propanol (120 μL, 1.56 mmol). The reaction was allowed to stir at 70 °C for 24 h. Upon completion by TLC

(40% ether/hexanes), the reaction was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed with water (20 mL). The aqueous layer was washed with ethyl acetate (3 × 30 mL), and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel.

General Procedure for Thiazolium-Catalyzed Acylsilane Additions to *N*-Phosphinoylimines. A screw-capped tube was charged with the thiazolium salt (20 mg, 0.08 mmol) and placed under a positive pressure of nitrogen. Benzoyltrimethylsilane (84 mg, 0.47 mmol) in $CHCl_3$ (0.25 mL) was added by syringe followed by the addition of DBU (12 μL, 0.08 mmol). The reaction mixture was heated to 60 °C after which the phosphoryl imine (0.26 mmol) in $CHCl_3$ (0.25 mL) was added by syringe followed by the addition of 2-propanol (80 μL, 1.05 mmol). The reaction was allowed to stir at 60 °C. Upon completion by HPLC, the reaction was cooled to room temperature, diluted with methylene chloride (20 mL), and washed with water (20 mL). The aqueous layer was washed with methylene chloride (3 × 30 mL), and the combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel.

General Procedure for Thiazolium-Catalyzed Pyrrole Synthesis. A screw-capped test tube was charged with the thiazolium salt (14 mg, 0.055 mmol, 0.20 equiv) and placed under a positive pressure of nitrogen. Benzoyltrimethylsilane (100 mg, 0.55 mmol, 2.0 equiv) in THF (0.25 mL) was added by syringe to the test tube followed by the addition of DBU (13 μL, 0.083 mmol, 0.30 equiv). The reaction mixture was heated to 70 °C after which the chalcone (0.275 mmol, 1.0 equiv) in THF (0.25 mL) was added by syringe followed by the addition of 2-propanol (83 μL, 1.10 mmol, 4.0 equiv). The reaction was allowed to stir at 70 °C for 12 h or until completion as determined by TLC (40% ether/hexanes). To the solution was added amine (0.825 mmol, 3.0 equiv) followed by addition of *p*-toluenesulfonic acid (104 mg, 0.55 mmol, 2.0 equiv) in ethanol (0.5 mL) and 4 Å molecular sieves (spatula tip). The reaction mixture remained heating at 70 °C for an additional 6 to 12 h or until consumption of diketone as determined by TLC (25% ethyl acetate/hexane). Upon cooling to room temperature, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (10 mL). The aqueous layer was washed with ethyl acetate (3 × 30 mL), and the combined organic extracts were washed with brine (10 mL) and dried over sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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