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Catalytic Additions of Acylsilanes to Imines: An Acyl Anion Strategy for the Direct Synthesis of α-Amino Ketones

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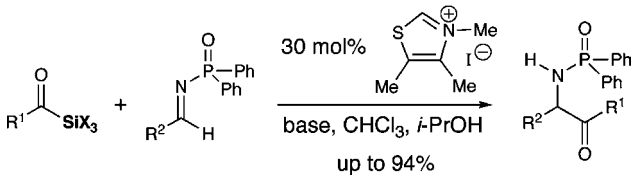
ABSTRACT



The addition of acylsilanes to imines catalyzed by neutral carbenes (or zwitterions) generated in situ from readily available thiazolium salts is described. The general reaction successfully utilizes acylsilanes as carbonyl anion precursors and is tolerant of a range of structural diversity on the acylsilane or imine electrophile. The overall reaction utilizes easily available precursors and directly accesses protected α-amino ketones in the correct oxidation state.

The synthesis of protected α-amino carbonyl compounds is an important goal due to the significant value of these compounds in synthetic and medicinal chemistry.[1] Additionally, these compounds are useful precursors for the synthesis of heterocycles[2] and 1,2-amino alcohols.[3] Although there are numerous catalytic methods to access α-amino acids, such as the Strecker reaction,[4] the direct synthesis of the related α-amino ketones in the desired oxidation state remains challenging.[5] While the stepwise modification of existing α-amino acids provides access to these molecules, a more direct and efficient construction of α-amino ketones is the addition of an acyl anion to an appropriately functionalized C=N system.

However, this *Umpolung* endeavor[6] requires that the reactivity of the imine, acyl anion precursor (AAP), and acyl anion are properly balanced to avoid AAP self-condensation (benzoin condensation). In this respect, the use of aldehydes as AAPs typically affords significant amounts of benzoin formation, thereby complicating acyl anion reactions. A superior AAP would avoid self-condensation, thus facilitating the use of a wider range of electrophiles and broadly expand the general scope of catalytic acyl anion addition reactions. Herein, we disclose that acylsilanes (**1**, X = SiR_3) engage in additions to readily available imines (**2**, Y = $P(O)R_2$) upon exposure to catalytic quantities of neutral nucleophilic species

(1) (a) Di Gioia, M. L.; Leggio, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *J. Org. Chem.* **2001**, *66*, 7002−7007 and references therein. (c) Beguin, C.; Andurkar, S. V.; Jin, A. Y.; Stables, J. P.; Weaver, D. F.; Kohn, H. *Bioorg. Med. Chem.* **2003**, *11*, 4275−4285. (d) Haustein, K. O. *Int. J. Clin. Pharm. Ther.* **2003**, *41*, 56−66.

(2) (a) Sorrell, T. N.; Allen, W. E. *J. Org. Chem.* **1994**, *59*, 1589−1590. (b) Langer, P.; Bodtke, A. *Tetrahedron Lett.* **2003**, *44*, 5965−5967. (c) Frantz, D. E.; Morency, L.; Soheili, A.; Murry, J. A.; Grabowski, E. J. J.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 843−846.

(3) For reviews on the utility and synthesis of 1,2-amino alcohols from α-amino ketones, see: (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546.

(4) (a) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875−877. For recent enantioselective variants, see: (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279−1281. (c) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634−5635 and references therein.

(5) For examples of this strategy utilizing acylimines generated in situ, see: (a) Castells, J.; López-Calahorra, F.; Bassedas, M.; Urrios, P. *Synthesis* **1988**, 314−315. (b) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696−9697.

(6) (a) Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357−402. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−258. (c) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328.

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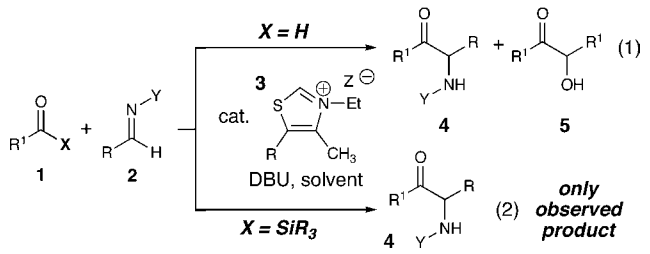
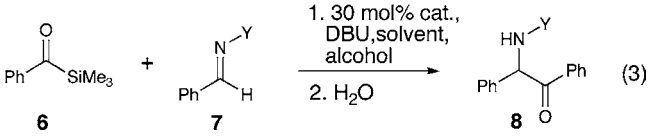
Scheme 1



accessed from thiazolium salts (**3**, Scheme 1, eq 2). This methodology enables direct formation of *N*-phosphinylated amino ketones (**4**) and completely avoids benzoin formation (**5**, Scheme 1, eq 1).

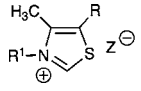
As part of a program focused on developing new strategies for accessing catalytic carbonyl anion chemistry using organocatalysis, we recently reported that carbenes/zwitterions from thiazolium salts are effective catalysts for the conjugate additions of acylsilanes (sila-Stetter).[7] This discovery generated a strong interest in combining this special acyl anion with additional electrophiles, thereby accessing additional unconventional carbon−carbon bond constructions. To test the feasibility of the proposed transformation, the addition of acylsilane **6** to various electrophilic azomethines in the presence of selected conditions was performed (Table 1). Surprisingly, although the *N*-sulfonylimine

Table 1. Optimization of Acylsilane Additions to Imines[a]



entry	Y	catalyst	solvent	alcohol	yield[b] (%)
1	SO_2Ph	**9**	THF	*i*-PrOH	NR[c]
2	$POPh_2$	**9**	THF	*i*-PrOH	69
3	$POPh_2$	**9**	CH_2Cl_2	*i*-PrOH	41
4	$POPh_2$	**9**	$CHCl_3$	*i*-PrOH	79
5	$POPh_2$	**9**	$CHCl_3$	*t*-BuOH	74
6	POPh	**10**	CHCl	*i*-PrOH	93

[a] Reactions performed at 0.5 M at reflux. [b] Isolated yield after chromatographic purification. [c] No reaction.

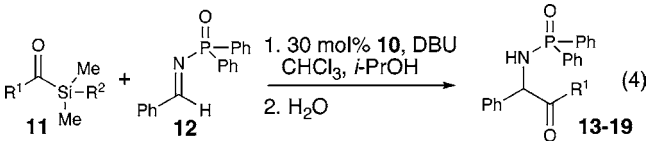


9: R = $(CH_2)_2OH$, R^1 = Et, Z = Br
10: R, R^1 = Me, Z = I

(**7**, Y = SO_2Ph) afforded no desired product (entry 1), the related *N*-diarylphosphinoylimines undergo smooth acyl anion addition of acylsilanes.[8] Following an extensive survey of solvents, additives, and bases, it was found that thiazolium salt **10** in chloroform with DBU as base and 2-propanol as alcohol additive provided the best yields for the desired α-amino ketone **8** (Y = $POPh_2$, 93%, entry 6). In contrast, the corresponding reaction with **10** and benzaldehyde as the AAP afforded poor yields of **8** due to significant contamination of benzoin. Interestingly, the use of nucleophilic *N*-heterocyclic carbenes derived from imidazolium and triazolium salts[9] did not afford any desired product.

With this viable catalytic system for the delivery of acyl anions identified, a brief survey of acylsilanes was conducted (Table 2, eq 4). The thiazolium-catalyzed addition of

Table 2. Survey of Acylsilanes[a]



entry	R^1	R^2	yield[b] (%)	product
1	Ph	Me	93	**13**
2	4-ClPh	Me	90	**14**
3	4-MePh	Me	81	**15**
4	Me	Me	87	**16**
5	Me	Ph	83	**16**
6	*n*-pentyl	Ph	71	**17**
7	$BnO(CH_2)_3$	Ph	63	**18**
8	*i*-Pr	Ph	51[c]	**19**

[a] For a representative procedure, see ref 9. [b] Isolated yield after purification. [c] At 90% conversion.

acylsilanes to imines can accommodate either alkyl or aryl acylsilane structures, thereby affording the desired ketones in excellent yield. However, acylsilanes with α-branching require higher catalyst loadings and longer reaction times to undergo complete conversion (entry 8). This attenuated reactivity may be due to the steric congestion that the zwitterion catalyst encounters when approaching the acylsilane carbonyl unit.

The influence of imine structure on the reaction has been examined (Table 3, eq 5). The reaction provides high yields of addition products with various substituted aryl imines. In addition, the process can accommodate electron-rich or electron-deficient systems. With substitution at the 2 position of the aryl ring (entry 10), the reaction affords the desired amino ketones in good yield, albeit at a slower rate (48 h vs 24 h). Presumably, this is due to the increased steric hindrance the incoming acyl anion nucleophile encounters. Imines derived from enolizable aldehydes undergo the known process of isomerization to the enamide and are thus far unproductive substrates.[10]

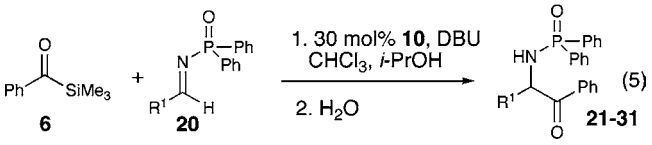
(7) (a) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314−2315. (b) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465−2468. For additional recent investigations of acylsilanes as acyl anions, see: (c) Xin, L. H.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534−2536. (d) Xin, L. H.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070−3071.

(8) (a) Krzyzanowska, B.; Stec, W. J. *Synthesis* **1982**, 270−273. (b) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561−5568. For recent examples of *N*-phosphinoyl imines in enantioselective reactions, see ref 4c and references therein. Less activated azomethines (e.g., *N*-benzylimines) afforded no conversion.

(9) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541.

(10) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970−8972.

Table 3. Scope of Imine Electrophiles[a]

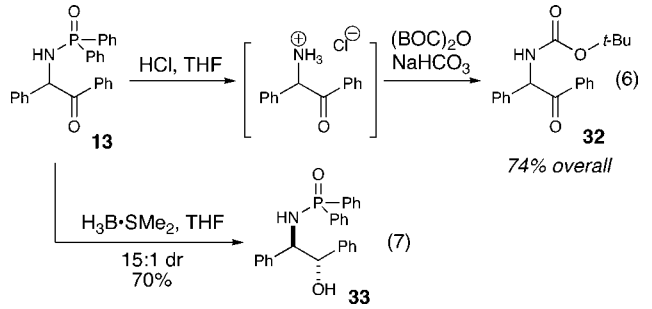


entry	R^1	yield[b] (%)	product
1	4-F-Ph	89	**21**
2	4-Cl-Ph	85	**22**
3	4-Br-Ph	82	**23**
4	4-Me-Ph	94	**24**
5	3-Me-Ph	83	**25**
6	4-OMe-Ph	86	**26**
7	2-OMe-Ph	70	**27**
8	2-Naphthyl	80	**28**
9	3,4-Cl-Ph	67	**29**
10	2-Cl-Ph	77[c]	**30**
11	2-thiophene	80	**31**

[a] For a representative procedure, see ref 9. [b] Isolated yield after chromatographic purification. [c] Reaction time 48 h for 100% conversion.

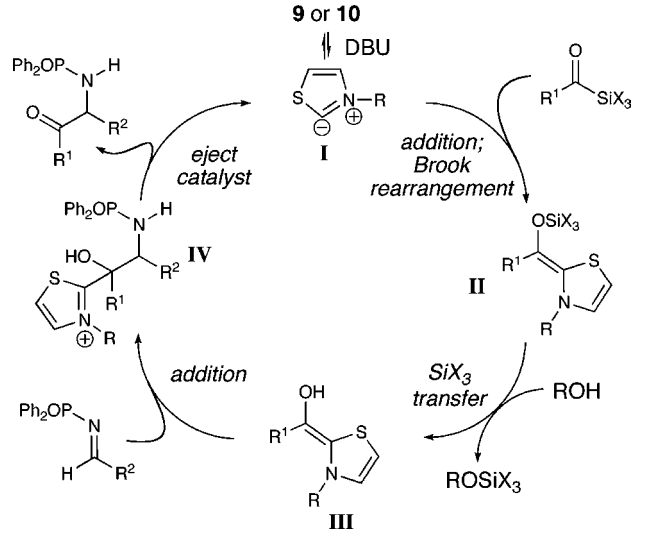
An attractive feature of this catalytic acyl anion process is that the resulting protected amines can be easily manipulated (Scheme 2). For example, the exposure of **13** to acid followed by $(BOC)_2O$ smoothly modulates the nitrogen protecting group in a one-flask operation (**32**, 74%, eq 6). Additionally, the addition of a reducing agent ($H_3B{\cdot}SMe_2$) produces the protected *trans*-1,2-amino alcohol **33** with high diastereoselectivity (15:1) and yield (70%, eq 7).[11]

Scheme 2



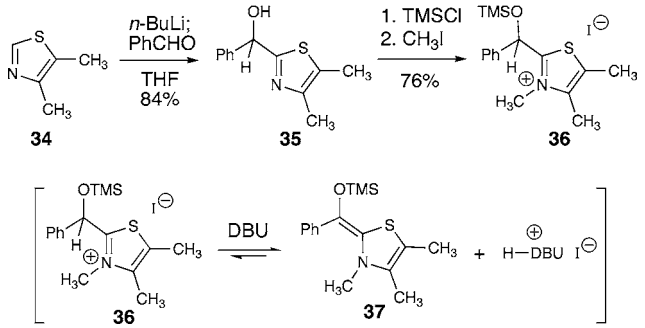
Our working reaction pathway is depicted in Scheme 3. The initial exposure of the thiazolium salt initiates the formation of the heterocyclic carbene/zwitterion catalyst species **I**.[12] This nucleophile undergoes addition to the acylsilane to generate intermediate **II** via a Brook rearrangement.[13] Presumably, catalyst addition to the imine substrate is reversible and thus unproductive. The resulting congested enolsilane undergoes conversion to **III** in the presence of 2-propanol and the resulting reduced steric environment around the double bond facilitates addition to the imine.[14] The collapse of this tetrahedral intermediate (**IV**) affords the desired ketone product with concomitant regeneration of the catalyst.[15]

Scheme 3. Proposed Catalytic Cycle



Although efforts toward the direct preparation and/or isolation of possible intermediates **II** or **III** have thus far been unrewarding, we have been able to prepare silyl ether **36** in order to probe the mechanism of the reaction (Scheme 4).[16] The initial lithiation of 4,5-dimethylthiazole followed by quenching with benzaldehyde afforded carbinol **35** in good yield (84%).[17] The subsequent silylation (TMS-Cl,

Scheme 4



(11) (a) Palmer, M. J.; Studley, J. R.; Walsgrove, T. C.; Wills, M. *Tetrahedron* **1998**, *54*, 8827−8840. (b) Fraser, D. S.; Park, S. B.; Chong, J. M. *Can. J. Chem.* **2004**, *82*, 87−101. See the Supporting Information for reaction details.

(12) For a review of thiamine-catalyzed processes, see: Pohl, M.; Lingen, B.; Müller, M. *Chem. Eur. J.* **2002**, *8*, 5289−5295. For a mechanistic discussion of thiazolium salts in the related benzoin reaction, see: (a) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241−8242. (b) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124−5131.

(13) (a) Brook, A. G.; LeGrow, G. E.; MacRae, D. M. *Can. J. Chem.* **1967**, *45*, 239−253. (b) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84. (c) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084.

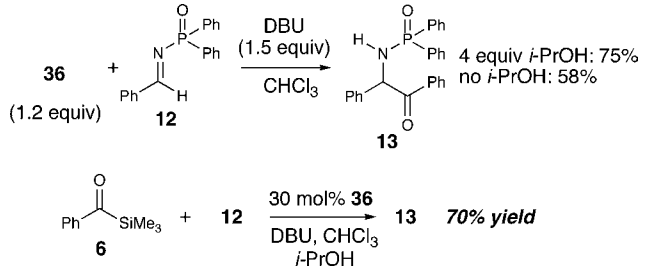
(14) Replacement of 2-propanol with 3-octanol affords 3-trimethylsilyloxyloctane (observed by GC), thus indicating that the alcohol is the silyl group acceptor. See the Supporting Information.

(15) An alternate pathway may involve direct addition of **II** to the imine followed by desilylation to turn over the catalyst and generate the product.

Et_3N) and methylation with MeI afforded the functionalized thiazolium salt **36** in 76% yield for the combined steps. To date, attempts to isolate enol silane **37** directly by deprotonation of **36** with strong base result in decomposition. However, we felt that exposure of **36** to the carbonyl anion reaction conditions (with DBU as base) might generate a sufficient concentration of **37** to participate as the putative carbonyl anion.

To test this hypothesis, 1.2 equiv of thiazolium salt **36** was combined with imine **12** (1.0 equiv) and DBU (1.5 equiv) in $CHCl_3$ at room temperature (Scheme 5). Gratifyingly, the desired protected α-amino ketone **13** was isolated in good yield with or without the use of 2-propanol. These results are not surprising since we have previously established that the alcohol additive is necessary for thiazolium catalyst turnover, not carbonyl anion reactivity.[18]

Scheme 5



In a second experiment, a catalytic quantity of silyl ether **36** was added to a mixture of acylsilane **6** and imine **12**. Although the product ketone (**13**) is produced in a lower yield (70%) than under normal catalytic conditions or when using a full equivalent of **36**, at least two turnovers have occurred. While these results indirectly implicate compounds with the general structure of **II** as intermediates in these carbonyl anion additions, it is apparent that a thiazolium zwitterion-initiated Brook rearrangement is an operative portion of the reaction mechanism.

In summary, we have discovered that readily available thiazolium salts in the presence of base promotes the addition of acylsilanes to *N*-diphenylphosphinoylimines. This new organocatalytic process rapidly generates useful α-amino ketones in the proper oxidation state from easily accessible imines. The protected α-amino ketones can be reduced in a highly diastereoselective manner and the phosphinoyl group on the nitrogen can be removed under mild conditions. Preliminary investigations of the reaction mechanism implicate that a thiazolium-catalyzed Brook rearrangement of acylsilanes initiates the carbonyl anion process. The further development of this nucleophile-catalyzed carbonyl anion strategy and related mechanistic investigations are currently underway.

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

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(16) No discernible intermediates could be identified by ^1H NMR (in $CDCl_3$) when combining acylsilane **6**, imine **12**, and thiazolium salt **10**.

(17) Barletta, G. L.; Zou, Y.; Huskey, W. P.; Jordan, F. *J. Am. Chem. Soc.* **1997**, *119*, 2356−2362.

(18) See references 7a and 7b.