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Azomethine Ylides from Tin-Substituted Cyclic Carbinol Amides: A New Route to Highly Substituted Pyrrolizidines

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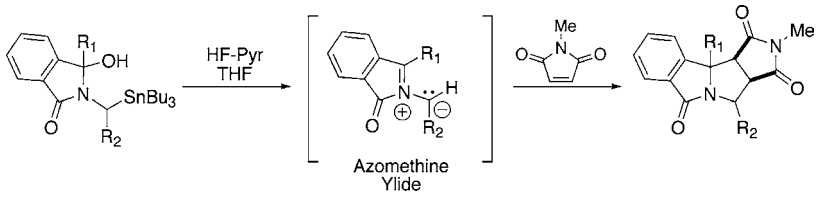
ABSTRACT



Addition of organolithium and organomagnesium reagents to *N*-(tri-*n*-butylstannylmethyl)phthalimides yields *N*-(tri-*n*-butylstannylmethyl) cyclic carbinol amides, which form azomethine ylides upon treatment with HF·pyridine. This novel route to azomethine ylides allows rapid access to highly functionalized pyrrolizidines (1,2,3,9b-tetrahydropyrrolo[2,1-*a*]isoindol-5-ones).

We have a longstanding interest in *N*-(tri-*n*-butylstannylmethyl)phthalimides[1] (e.g., **1**) as intermediates in the synthesis of (2-azaallyl)stannanes,[2] which are precursors to nonstabilized 2-azaallyllithiums[2a,c,3] and nonstabilized azomethine ylides[4] and also serve as α,α′-aminodication equivalents.[2b] We have also been interested in the chemistry of α-amino organolithiums generated by tin−lithium exchange of α-aminostannanes.[5] In the course of attempting to generate the novel α-amino organolithium **2** from *N*-(tri-*n*-butylstannylmethyl)phthalimide **1**, we observed that under typical tin−lithium exchange conditions (*n*-BuLi, −78 °C, THF) the addition of *n*-butyllithium to the imide group to give cyclic carbinol amide **3** is favored over tin−lithium exchange (Scheme 1). This observation is in contrast to the successful tin−lithium exchange of compounds bearing less electrophilic carbonyl groups such as ureas, carbamates, and amides.[1,5,6] It was subsequently found that **3** formed an azomethine ylide upon treatment with HF·pyridine, which underwent cycloaddition with *N*-methylmaleimide to form the pyrrolizidine cycloadduct **4** in excellent yield. Preliminary studies into the scope of this novel route to azomethine ylides and its application to a general synthesis of 1,2,3,9b-tetrahydropyrrolo[2,1-*a*]isoindol-5-one cycloadducts are described herein.

The process by which an azomethine ylide is believed to be formed from cyclic carbinol amide **3** is outlined in Scheme 1. Treatment of **3** with HF·pyridine in refluxing THF over 10 min induces the formation of *N*-acyliminium[7] **5**, which

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(1) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220−2222.

(2) (a) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903−921. (b) Pearson, W. H.; Aponick, A. *Org. Lett.* **2001**, *3*, 1327−1330. (c) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354−6356.

(3) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329−1345.

(4) (a) Pearson, W. H.; Clark, R. B. *Tetrahedron Lett.* **1999**, *40*, 4467−4471. (b) Clark, R. B.; Pearson, W. H. *Org. Lett.* **1999**, *1*, 349−351. (c) Pearson, W. H.; Mi, Y. *Tetrahedron Lett.* **1997**, *38*, 5441−5444. (d) Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, in press.

(5) (a) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622−2636. (b) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546−8548. (c) Pearson, W. H.; Lindbeck, A. C. *J. Org. Chem.* **1989**, *54*, 5651−5654.

(6) Some recent selected examples: (a) Christoph, G.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2189−2192. (b) Clayden, J.; Helliwell, M.; Pink, J. H.; Westlund, N. *J. Am. Chem. Soc.* **2001**, *123*, 12449−12457. (c) Iula, D. M.; Gawley, R. E. *J. Org. Chem.* **2000**, *65*, 6196−6201.

(7) *N*-Acyliminiums derived from cyclic carbinol amides have proved to be useful intermediates in the synthesis of nitrogen-containing heterocycles. See: Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 189−191 and references therein.

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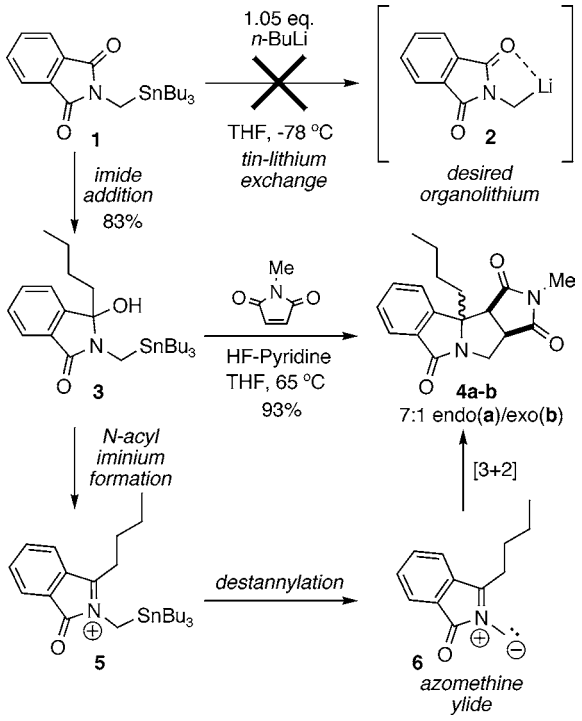
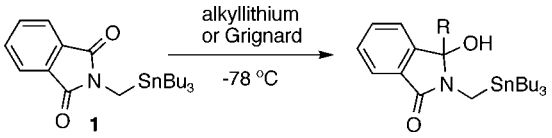
Scheme 1



is followed by destannylation to form a stabilized azomethine ylide **6**. Cycloaddition with *N*-methylmaleimide yields the final cycloadduct **4**. At room temperature this reaction runs a similar course but requires several hours to reach completion. Heating **3** in THF in the absence of HF·pyridine led to no reaction. Additionally, treatment of **3** with TBAF in refluxing THF yielded only slow decomposition, showing that fluoride alone is not responsible for azomethine ylide generation. Other electrophiles such as $3HF{\cdot}Et_3N$, $TiCl_4$, TiF_4, TMSCl, and PPTS were investigated in place of HF·pyridine, but all gave varying amounts of undesired enamide byproducts resulting from deprotonation of *N*-acyliminium intermediate **5**.

Although demetalation of *N*-(trimethylsilyl)methyl- or *N*-(tri-*n*-butylstannyl)methyl iminium salts has proved to be a useful way to generate azomethine ylides,[4,8] these iminium intermediates have never before been generated by the ionization of hemiaminals (*N*,*O*-hemiketals) such as **3**. Previously, Padwa, Achiwa, and Sakurai have shown that azomethine ylides can be formed from desilylation of *N*-(trimethylsilyl)methyl iminiums generated from the ionization of aminals (*N*,*O*-acetals).[9] Also relevant to our studies is the work of Achiwa,[10] who demonstrated that stabilized

Table 1. Addition of Organometallics to Phthalimide **1**



R-M	equiv	solvent	product	yield[a]
MeLi	1.1	Et_2O	**7**	93%
n-BuLi	1.05	THF	**3**	83%
n-BuLi	1.05	Et_2O	**3**	95%
i-PrLi	1.05	Et_2O	**8**	<10%
i-PrMgCl	1.1	Et_2O	**8**	86%
t-BuLi	1.2	Et_2O	**9**	47%
vinyl MgBr	1.1	Et_2O	**10**	82%
allyl MgBr	1.1	Et_2O	**11**	97%
PhLi	1.1	Et_2O	**12**	0%
PhMgBr	1.5	Et_2O	**12**	93%

[a] Isolated yields after column chromatography.

azomethine ylides could be formed from phenyl-substituted (2-azaallyl)silanes by quaternization of the imine with benzoyl chloride, followed by desilylation of a *N*-(trimethylsilyl)methyl-substituted *N*-acyliminium. However, Achiwa's method appears not to tolerate enolizable hydrogens, as are present in our case.

The 1,2,3,9b-tetrahydropyrrolo[2,1-*a*]isoindol-5-one ring system produced in this cycloaddition process (e.g., **4**) has been the subject of a variety of synthetic studies.[11] Of particular note is the work of Yoon and Mariano,[12] who have investigated the formation of azomethine ylides from *N*-(trimethylsilylmethyl)phthalimides and *N*-phthaloyl-α-amino acids using photochemical means to form cycloadducts similar to **4** but bearing a hydroxy or silyloxy substituent at the bridgehead position. In contrast, our method gives cycloadducts with carbon-based substituents at the bridgehead. Formation of such quaternary carbon bridgehead-substituted pyrrolizidines by azomethine ylide cycloadditions is very rare.[13]

To examine the scope of bridgehead substitution possible in the pyrrolizidine cycloadducts, we first investigated the addition of various organometallics to phthalimide **1** (Table 1). Although addition of *n*-butyllithium to **1** proceeds well in THF, the use of diethyl ether cleanly gave **3** in higher yield without any trace of tin−lithium exchange.[14] While

(8) (a) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; pp 169−252. (b) Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, *27*, 981−1008. (c) Vedejs, E. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich; CT, 1988; Vol. 1, pp 33−51. (d) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941−955.

(9) (a) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235−244. (b) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 896−898 and 2762−2766. (c) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117−1120.

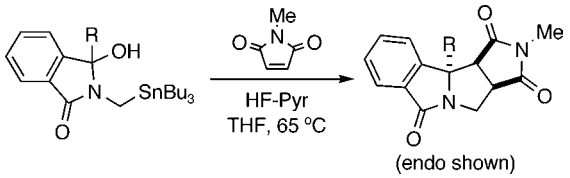
(10) See ref 8b and: Achiwa, K.; Sekiya, M. *Chem. Lett.* **1981**, 1213−1216.

(11) For recent synthetic work, see: (a) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525−7539. (b) Reyes, A.; Regla, I.; Fragoso, M. C.; Vallejo, L. A.; Demare, P.; Jimenez-Vazquez, H. A.; Ramirez, Y.; Juaristi, E.; Tamariz, J. *Tetrahedron* **1999**, *55*, 11187−11202. (c) Luzzio, F. A.; Zacherl, D. P. *Tetrahedron Lett.* **1998**, *39*, 2285−2288. (d) Ha, D.-C.; Yun, C.-S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577−2580. (e) Grigg, R.; Sriharan, V.; Suganthan, S.; Bridge, A. W. *Tetrahedron* **1995**, *51*, 295−306. This ring system has also appeared in studies of cyclin-depedent kinase (Cdk4) inhibitors: (f) Honma, T.; Hayashi, K.; Aoyama, T.; Hashimoto, N.; Machida, T.; Furasawa, K.; Iwama, T.; Ikeura, C.; Ikuta, M.; Suzuki-Takahashi, I.; Iwasawa, Y.; Hayama, T.; Nishimura, S.; Morishima, H. *J. Med. Chem.* **2001**, *44*, 4615−4627 and references therein.

methyllithium and *tert*-butyllithium also added to **1** in useful yields, isopropyllithium and phenyllithium gave mostly decomposition. In these cases, the corresponding Grignard reagents gave excellent yields of cyclic carbinol amides **8** and **12**. The addition of vinyl and allyl Grignard reagents to **1** also proceeded smoothly. The unsubstituted cyclic carbinol amide **13** was obtained by partial reduction of **1** with sodium borohydride.[15]

With cyclic carbinol amides **3** and **7**−**13** in hand, we subjected them to standard cycloaddition conditions (Table 2). Good to excellent yields of cycloadducts were obtained, notably even in the case of sterically demanding substituents such as isopropyl or *tert*-butyl. The cycloadditions were all highly endo selective, which is typical for this type of stabilized azomethine ylide.[12d] In contrast, nonstabilized azomethine ylides derived from destannylation of (tri-*n*-butylstannyl)methyl iminiums typically give very poor exo/endo selectivity.[4]

Table 2. Cycloaddition to Form Various Bridgehead-Substituted Pyrrolizidines



starting material	R	product	yield[a]	endo(**a**)/exo(**b**)
13	H	**14a**,**b**	82%[b]	78:22
7	Me	**15**	68%	100:0
8	*i*-Pr	**16**	82%	100:0
3	*n*-Bu	**4a**,**b**	93%	86:14
9	*t*-Bu	**17a**,**b**	81%	85:15
10	vinyl	**18**	82%	100:0
11	allyl	**19**	65%	100:0
12	Ph	**20**	71%	100:0

[a] Isolated yields after column chromatography. [b] Required 2.5 h to consume all starting material, which typically took only 10−20 min in most other cases.

To further explore the substitution patterns possible in the pyrrolizidine cycloadducts, cyclic carbinol amides **24**−**26** were synthesized bearing substitution adjacent to the tri-*n*-butylstannyl moiety (Scheme 2). Addition of *n*-butyllithium

Scheme 2

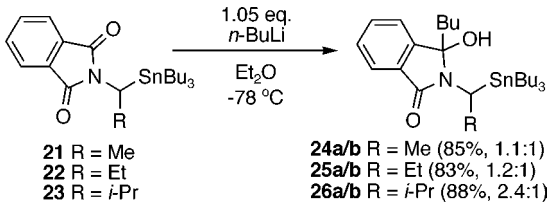
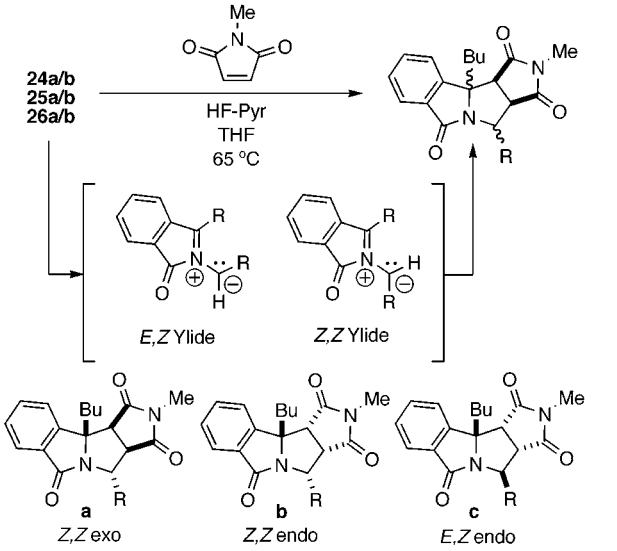


Table 3. Exploring 1,3-Disubstituted Azomethine Ylides



starting material	R	product	yield[a]	**a**[b]	**b**[b]	**c**[b]
24a	Me	**27a**−**c**	65%	1	3.6	2.9
24b	Me	**27a**−**c**	80%	1	13	3.6
25a	Et	**28a**−**c**	83%	1	3.1	2.3
25b	Et	**28a**−**c**	77%	1	2.6	1.9
26a	*i*-Pr	**29a**−**c**	49%	1	19	5
26b	*i*-Pr	**29a**−**c**	23%	1	9	13

[a] Isolated yields after column chromatography. [b] Ratios of diastereomers **a**−**c** in isolated products corresponded with those in the crude ^{1}H NMR spectra.

to known phthalimides **21**−**23**[1,2c] in ether gave two separable diastereomers of **24**−**26**. Unfortunately, the relative configuration of these diastereomers could not be conclusively assigned.

Treatment of **24**−**26** with HF·pyridine in refluxing THF gave highly substituted pyrrolizidines **27**−**29** in moderate to excellent yields (Table 3). In principle, both diastereomers of **24**−**26** should give rise to a common azomethine ylide intermediate, leading to similar cycloaddition outcomes. However, some differences in yields and diastereomeric ratios were observed for **27**−**29**, which are difficult to rationalize without knowledge of the stereostructure of the

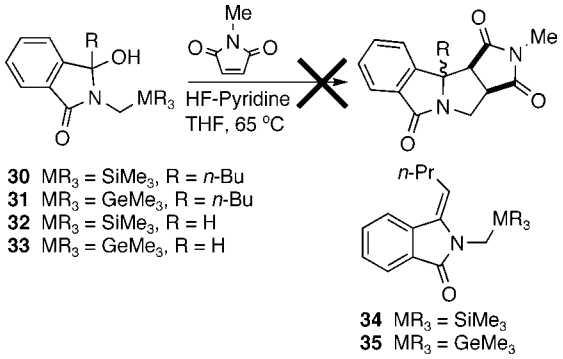
(12) (a) Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **2001**, *34*, 523−533. (b) Takahashi, Y.; Miyashi, T.; Yoon, U. C.; Oh, S. W.; Mancheno, M.; Su, Z.; Falvey, D. F.; Mariano, P. S. *J. Am. Chem. Soc.* **1999**, *121*, 3926−3932. (c) Yoon, U. C.; Lee, C. W.; Oh, S. W.; Mariano, P. S. *Tetrahedron* **1999**, *55*, 11997−12008. (d) Yoon, U. C.; Kim, D. U.; Lee, C. W.; Choi, Y. S.; Lee, Y.-J.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1995**, *117*, 2698−2710. (e) Yoon, U. C.; Cho, S. J.; Lee, Y.-J.; Mancheno, M. J.; Mariano, P. S. *J. Org. Chem.* **1995**, *60*, 2353−2360.

(13) For examples of bridgehead substitution in 1-aza[*m*.3.0]bicycloalkanes derived from the intermolecular cycloaddition of azomethine ylides, see ref 4c and: (a) Epperson, M. T.; Gin D. Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1778−1780. (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475−2486. (c) Felluga, F.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2331−2335.

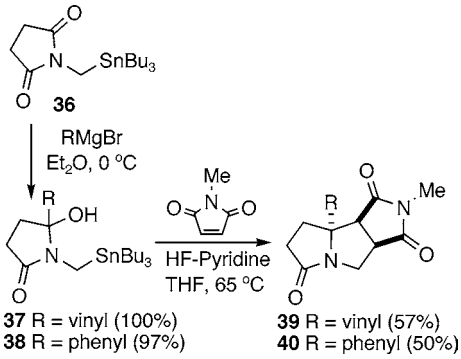
(14) When THF was used as the solvent, about 5−10% tin−lithium exchange occurred as judged by isolation of Bu_4Sn.

(15) Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, *24*, 1407−1410.

Scheme 3



Scheme 4



starting carbinol amides **24**−**26**. A slight preference for (*Z*,*Z*)-ylide-derived cycloadducts was observed in most cases. This preference may be due to unfavorable steric interactions between the R groups in the conformation the iminium intermediates require for destannylation to the (*E*,*Z*)-ylide (i.e., the Sn−C bond should be parallel to the iminium π-system).

In addition to tri-*n*-butylstannane **3**, we have also studied trimethylsilyl- and trimethylgermyl-substituted cyclic carbinol amides **30**−**33** under our standard HF·pyridine cycloaddition conditions (Scheme 3). No cycloadducts were isolated in these experiments. Instead, compounds **30** and **31** gave enamides **34** and **35** in 75 and 69%, respectively, while compounds **32** and **33** gave only slow decomposition. Apparently, the Sn−C bond in iminium **5** is much weaker than the analogous Si−C and Ge−C bonds and is readily destannylated to form azomethine ylide **6**. The lability of the Sn−C bond in **5** relative to the Si−C and Ge−C versions may be related to the much larger β-element effect of tin relative to silicon and germanium.[16] A greater hyperconjugative interaction between the Sn−C bond and the neighboring electron-deficient iminium π-system in **5** should weaken the Sn−C bond, leading to facile destannylation by fluoride to form **6**. Analogous hyperconjugation of Si−C, Ge−C, and Sn−C bonds with neighboring oxonia cations has been investigated by Linderman[17] and Rychnovsky.[18]

Finally, we have begun exploring the suitability of cyclic carbinol amides besides phthalimides in the cycloaddition process (Scheme 4). Cyclic carbinol amides **37** and **38** were cleanly formed from succinimide **36** by the addition of vinyl and phenyl Grignard reagents. Treatment with HF·pyridine in refluxing THF induced cycloaddition with *N*-methylmaleimide to give moderate yields of pyrrolizidines **39** and **40** exclusively as the endo diastereomers. We have not yet had success inducing cycloaddition in succinimide-derived substrates that bear hydrogen or simple alkyl substitution in place of the vinyl and phenyl groups of **37** and **38**.

In conclusion, we have discovered a novel route to stabilized azomethine ylides through the ionization and destannylation of *N*-(tri-*n*-butylstannylmethyl) cyclic carbinol amides. The resulting 1,3-dipoles undergo cycloaddition with electron-deficient dipolarophiles to give highly substituted pyrrolizidines. We are currently further investigating the scope and mechanism of this reaction, including intramolecular variants.

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Supporting Information Available: Preparative procedures, characterization data, ^{1}H NMR, and selected ^{1}H−^{1}H COSY NMR spectra for **3**, **4a**,**b**, **13**, **14a**,**b**, **25a**,**b**, **28a**−**c**, **30**−**33**, **36**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) β-Element effect of tin is at least 10^4 times that of silicon and 10^3 times that of germanium; see: (a) Hagan, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954−4961. (b) Lambert, J. B.; Wang, G−t.; Teramura, D. H. *J. Org. Chem.* **1988**, *53*, 5422−5428. (c) Traylor, T. G.; Koermer, G. S. *J. Org. Chem.* **1981**, *46*, 3651−3657.

(17) (a) Linderman, R. J.; Chen, K. *J. Org. Chem.* **1996**, *61*, 2441−2453. (b) Linderman, R. J.; Anklekar, T. V. *J. Org. Chem.* **1992**, *57*, 5078−5080.

(18) (a) Cossrow, J.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 147−150. (b) Rychnovsky, S. D.; Cossrow, J. *Org. Lett.* **2003**, *5*, 2367−2370. (c) Huckins, J. R.; Rychnovsky, S. D. *J. Org. Chem.* **2003**, *68*, 10135−10145.