Title

Asymmetric Electrophilic α-Amination of Silyl Enol Ether Derivatives via the Nitrosocarbonyl Hetero-ene Reaction

Journal

Organic Letters, 17(18)

ISSN

1523-7060

Authors

Sandoval, David
Samoshin, Andrey V
de Alaniz, Javier Read

Publication Date

2015-09-18

DOI

10.1021/acs.orglett.5b02208

Peer reviewed

Organic LETTERS

Letter

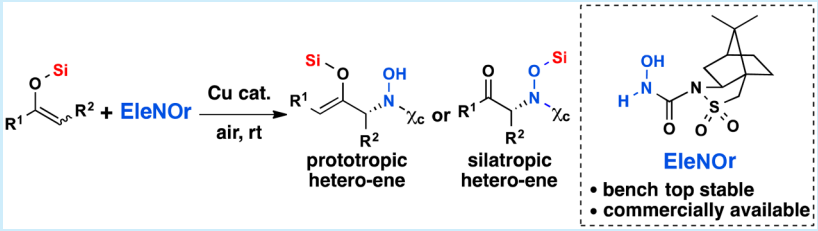
pubs.acs.org/OrgLett

Asymmetric Electrophilic α-Amination of Silyl Enol Ether Derivatives via the Nitrosocarbonyl Hetero-ene Reaction

David Sandoval, Andrey V. Samoshin, and Javier Read de Alaniz*

Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States

Supporting Information



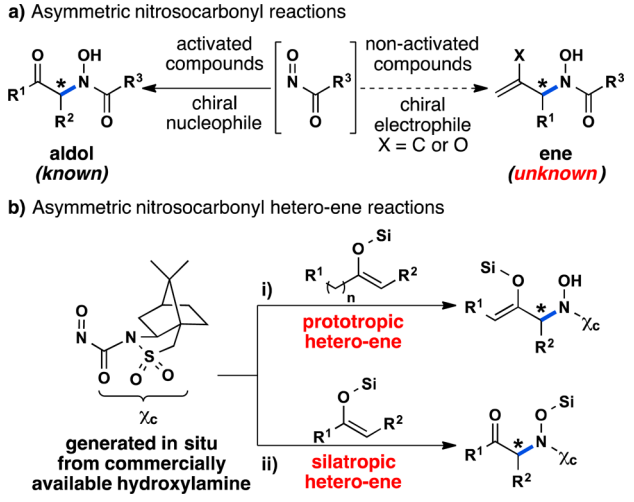
ABSTRACT: The first example of a general asymmetric nitrosocarbonyl hetero-ene reaction is described. The procedure uses a copper-catalyzed aerobic oxidation of a commercially available chiral nitrosocarbonyl precursor (EleNOr) and is operationally simple. The transformation is both high yielding and highly diastereoselective for a range of silyl enol ether derivatives. A variety of synthetically useful postfunctionalization reactions are presented along with a mechanistic rationale that can be used as a predictive model for future asymmetric reactions with nitrosocarbonyl intermediates.

The asymmetric construction of C−N bonds using in situ generated nitrosocarbonyl intermediates has recently experienced rapid development, particularly in the area of the nitrosocarbonyl aldol reaction.[1,2] This emerging area of research has relied on the development of new, mild, and functional group compatible oxidation protocols of hydroxamic acids to gain access to highly reactive nitrosocarbonyl intermediates.[3,4] While promising, these current strategies are limited to the use of activated compounds (β-ketoesters and aldehydes) where the stereodirecting group is placed on the backbone of the nucleophile using known chiral Lewis acids or chiral organocatalysts.[5] Alternatively, placement of the chirality on the nitrosocarbonyl could allow access to a more general range of asymmetric transformations, including the use of nonactivated compounds (ketone and carboxylic acid derivatives) via the nitrosocarbonyl hetero-ene reaction (Scheme 1a).[6b,e,7,3b]

Silyl enol ethers and silyl ketene thioacetals are known to undergo asymmetric hetero-ene reactions with aldehydes.[8,9] These are commonly referred to as the Mukaiyama aldol reaction, for which a prototropic or silatropic mechanism has been invoked. Silyl enol ethers derivatives bearing allylic hydrogens are known to proceed through a prototropic mechanism,[8] and in their absence, the silatropic pathway becomes favored.[9,8g] Despite the significant potential, no asymmetric aza-variant using nitroso compounds has been developed. Herein we report an asymmetric nitrosocarbonyl hetero-ene reaction with silyl enol ether derivatives (Scheme 1b).[10]

Nitrosobenzene is known to react with silyl enol ethers in a racemic fashion;[11] however, attempts to render this process asymmetric result in the exclusive reaction on oxygen (α-oxylation).[12] Given the prevalence of α-amino carbonyl compounds in medicinal chemistry and the broad synthetic utility of silyl enol ethers, we sought to develop an asymmetric nitrosocarbonyl hetero-ene reaction. This strategy simultaneously enables the direct asymmetric formation of C−N bonds α to nonactivated carbonyl compounds[5,13] and establishes a precedent for a general asymmetric nitrosocarbonyl hetero-ene reaction. Moreover, as the nitro-

Scheme 1. α-Functionalization of Carbonyl Compounds via the Hetero-ene Reaction

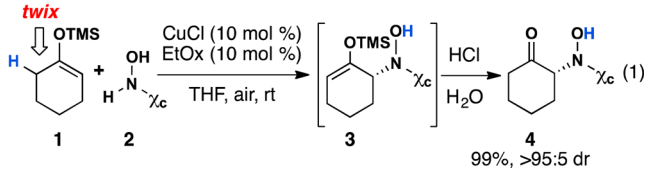


Received: July 29, 2015
Published: August 28, 2015

DOI: 10.1021/acs.orglett.5b02208
Org. Lett. 2015, 17, 4514−4517

socarbonyl ene reaction is selective for C−N bond formation,[6d] this process does not suffer the same *O*- vs *N*-regioselectivity drawbacks as the nitrosocarbonyl aldol reaction.

Our experience with nitrosocarbonyl aldol[1a,2b] and ene reactions,[3b] combined with the established *twix* enophilic regioselectivity of nitrosobenzene with trisubstituted olefins,[14] led us to commence studies with the TMS-enol ether derived from cyclohexanone (**1**) and a hydroxamic acid derived from Oppolzer's sultam (**2**).[15,16] To our gratification, we found that running the reaction with 10 mol % of CuCl and 10 mol % of 2-ethyloxazoline resulted in a nearly quantitative yield of the desired product with excellent diastereoselectivity (eq 1); see



the Supporting Information for optimization studies). While the hetero-ene adduct (**3**) can be isolated in 69% yield and >95:5 dr (see the Supporting Information), a hydrolytic workup was used to aid in isolation and characterization of the product. Formation of the competitive *O*-regioisomer was not observed, which is in accord with the nitrosocarbonyl ene reaction.[6e]

Having established the optimized reaction conditions (10 mol % of CuCl, 10 mol % of EtOx, THF, air, rt), attention was then turned toward the scope of this transformation (Figure 1). Cyclic aliphatic silyl enol ethers, all possessing an *E*-enolate geometry, afford good yields and excellent diastereoselectivities (**4**, **7**, and **8**). To our gratification, the use of acyclic silyl enol ethers derived from 3-pentanone gave high yields and good diastereoselectivities regardless of the *E*/*Z* geometry (**9** and **10**). The use of the *E*-silyl enol ether (75:25 *E*/*Z*) afforded the desired product in a 75:25 diastereoselectivity, whereas the *Z*-silyl enol ether (80:20 *E*:*Z*) yielded the desired product with a 91:9 diastereoselectivity. Importantly, the products of these reactions were enriched in the same major diastereomer. An improved diastereoselectivity could be obtained with substrate **11**, which can easily be accessed from the *Z*-silyl enol ether (5:95 *E*/*Z*). On the basis of these findings, we hypothesized that the reaction would be highly diastereoselective for aryl-derived *Z*-silyl enol ethers lacking the allylic hydrogen atom. Indeed, switching to the naphthyl-derived *Z*-silyl enol ether led to **12** in 86% yield and 91:9 dr. Moreover, a variety of substituted aryl *Z*-silyl enol ethers afforded good yields and diastereoselectivities (**13**−**16**). Notably, this transformation is also amenable to the use of heteroaromatic silyl enol ethers as well (**17**−**19**). In these cases, the 2-pyridyl substrate (**17**) gave a better yield of the desired product, while the 4-pyridyl substrate (**18**) was more diastereoselective. The lower yield for **18** was due to product instability. The furan substrate was well tolerated and afforded the desired product with excellent diastereoselectivity (**19**). Lastly, we explored the use of cyclic aromatic *E*-silyl enol ethers, which as expected lead to reduced diastereoselectivities, albeit with good isolated yields (**20** and **21**). These results suggest that *Z*-silyl enol ethers lacking an allylic hydrogen are critical for high selectivity, which is consistent with the nature of the proposed silatropic nitrosocarbonyl hetero-ene reaction (vide infra). It is worth noting that dehydration of the products to the α-imine is conceivable and known, but we did not observe the formation of this product.[6d]

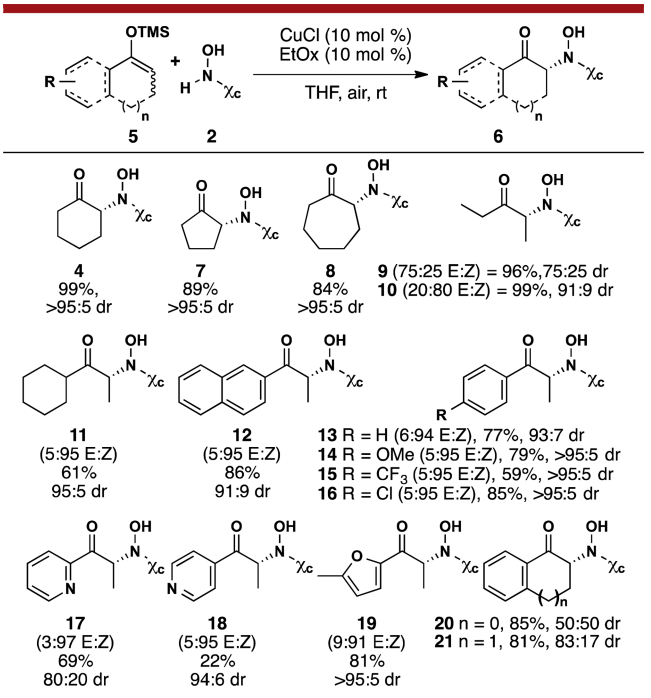


Figure 1. Scope of asymmetric nitrosocarbonyl hetero-ene reaction. All reactions were performed with 1 equiv of **2** and 1.2 equiv of **5**. Yields are shown. dr is calculated by ^{1}H NMR. EtOx = 2-ethyloxazoline.

Encouraged by these results and the mildness of the reaction conditions, we sought to expand on this reaction with the use silyl ketene thioacetals.[17] Given that thioesters are readily amenable to a variety of postfunctionalization reactions,[18] and the breadth of literature on forming their respective enolate geometries,[19] their use here further broadens the synthetic utility of this approach. Analogous to the ketone substrates, it was found that this silatropic nitrosocarbonyl hetero-ene reaction was most favored with substrates bearing an *E*-enolate geometry (Figure 2).[20,21] Of note, the reaction to form **28** was conducted on a 2 mmol scale. Importantly, the yield and diastereoselectivity for this reaction was not affected, which highlights the potential scalability of this process. In addition, it was discovered that 2 equiv of the nucleophile could be used to obtain products with high diastereoselectivity when a 1:1 mixture of *E*/*Z* silyl ketene thioacetals are used (**29**). This result provides an attractive solution to situations where access to the desired *E*-silyl ketene thioacetal is challenging. It is envisioned that these products can be used to access non-natural amino acid derivatives and their hydroxylamino analogues, such as D-Ala, D-Leu, D-Trp, D-Phe, and D-Val with high stereoinduction (>95:5 dr for **25**−**28** and 92:8 dr for **29**). While *N*-hydroxyamino acid derivatives are relatively uncommon in nature, they are of great biological importance.[22] For example, the availability of optically active *N*-hydroxyamino acids is of particular importance for the synthesis of *N*-hydroxypeptides[23,24] and siderophores,[25] as well as amide-forming ligation reactions.[26]

With a broad substrate scope established, we next sought to develop a predictive model for the asymmetric nitrosocarbonyl hetero-ene reaction. Analogous to the nitrosobenzene hetero-ene reaction with trisubstituted olefins, the asymmetric nitrosocarbonyl hetero-ene reaction with silyl enol ethers

DOI: 10.1021/acs.orglett.5b02208
Org. Lett. 2015, 17, 4514−4517

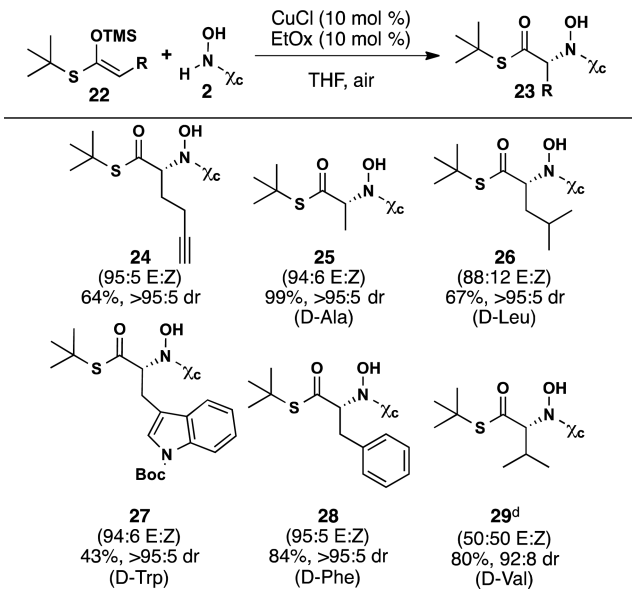
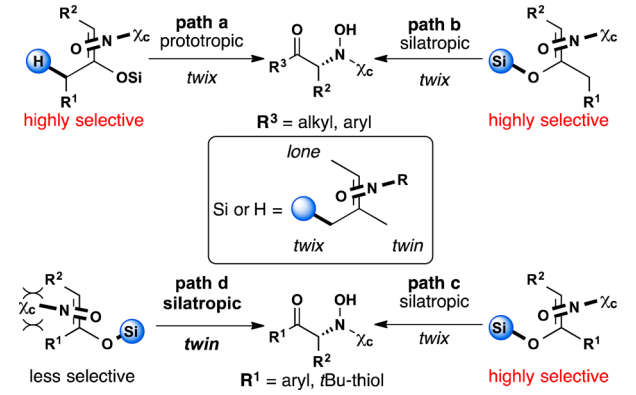


Figure 2. Scope of the asymmetric nitrosocarbonyl hetero-ene reaction with silyl ketene thioacetals. All reactions were performed with 1 equiv of **2** and 1.5 equiv of **22**. Yields are shown. dr is calculated by ^{1}H NMR. 2 equiv of **22** was used. EtOx = 2-ethyloxazoline.

follows the same enophilic regioselectivity for the *twix* position (Scheme 2).[6b,7b,d,14a−e] For substrates with allylic hydrogens

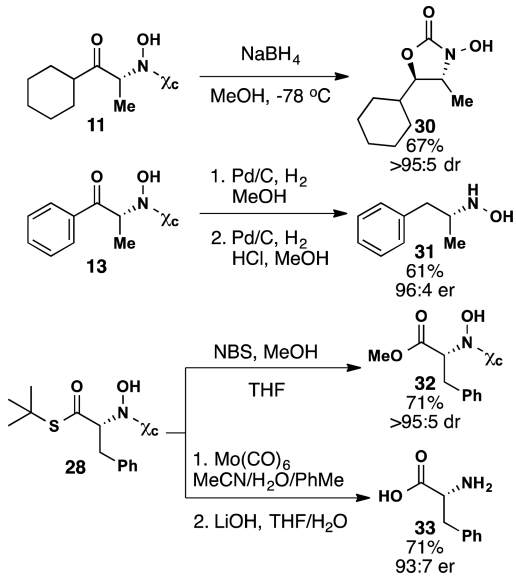
Scheme 2. Mechanism and Predictive Model



and an *E*-enolate geometry (**4**, **7**−**9**), the *twix* selective prototropic pathway is favored because the nitrosocarbonyl adopts a *Re*-face *skew* approach toward the nucleophile, which minimizes steric interactions (path a). With the *Z*-enolate geometry, the *twix* position is now located at the oxygen atom bearing the TMS group (**10** and **11**), and the silatropic pathway becomes favored (path b). The nitrosocarbonyl still adopts the same *skew* trajectory toward the *Re* face of the nucleophile with minimized steric interactions and as such affords products with the same absolute stereochemistry. For substrates lacking allylic hydrogens, a *twix*-selective silatropic pathway was found to be most favorable (**12**−**29**) and again was attributed to the minimized steric interactions of the *Re*-face *skew* approach of the nitrosocarbonyl (path c). The lower diastereoselectivities observed with substrates lacking allylic hydrogens (**20** and **21**) are attributed to increased steric interactions of a *twin*-selective silatropic pathway where the nitrosocarbonyl approaches the nucleophile with decreased facial bias (path d).

To illustrate the synthetic utility of this methodology and demonstrate that the auxiliary can be removed, a series of postfunctionalization reactions were studied (Scheme 3).

Scheme 3. Transformations of α-Amino Carbonyls



Enantiopure *N*-hydroxyoxazolidinone **30** could be obtained from **11** through a diastereoselective reduction using sodium borohydride. Chiral oxazolidinones are an important class of ligands in asymmetric catalysis[27] and have interesting biological activity.[28] Additionally, the *N*-hydroxyphenethylamine **31** can be obtained in one step using a hydrogenation of chiral α-amino ketone **13** in high yield and enantiopurity, with quantitative recovery of the sultam. Although not shown, the N−O bonds of the ketone derived products are also readily cleaved.[29] Treatment of thioester **28** with NBS and MeOH affords the methyl ester **32** in high yield, without racemization. Finally, a two-step sequence can also be performed wherein N−O bond homolysis is followed by saponification, yielding **33**.

In conclusion, a novel and highly diastereoselective nitrosocarbonyl hetero-ene reaction was demonstrated utilizing a mild aerobic oxidation of a chiral nitrosocarbonyl precursor that is commercially available. The reaction was applicable to a broad range of substrates to afford products in high yields with excellent diastereoselectivities. In addition, the reaction is completely *N*-selective. The array of functionalization possibilities and the predictive model, both described here in detail, render this a practical entry into a variety of previously inaccessible chiral hydroxylamines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02208.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: javier@chem.ucsb.edu.

DOI: 10.1021/acs.orglett.5b02208
Org. Lett. 2015, 17, 4514−4517

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from UCSB and Amgen is gratefully acknowledged. We thank Dr. Guang Wu (UCSB) for X-ray analysis. We also thank Patrick Batoon and O. David Sparkman of the University of the Pacific Mass Spectrometry facility and Professor Martin Schnermann for helpful discussions. NMR instrumentation was supported by an NIH Shared Instrumentation grant (SIG) (No. 1S10OD012077-01A1).

■ REFERENCES

(1) For the *N*-selective nitrosocarbonyl aldol, see: (a) Sandoval, D.; Frazier, C. P.; Bugarin, A.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2012**, *134*, 18948. (b) Kano, T.; Shirozu, F.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 18036. (c) Selig, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7080. (d) Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8714. (e) Kano, T.; Shirozu, F.; Maruoka, K. *Org. Lett.* **2014**, *16*, 1530. (f) Xu, C.; Zhang, L.; Luo, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 4149. (g) Maji, B.; Baidya, M.; Yamamoto, H. *Chem. Sci.* **2014**, *5*, 3941.

(2) For the *O*-selective nitrosocarbonyl aldol, see: (a) Baidya, M.; Griffin, K. A.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 18566. (b) Frazier, C. P.; Sandoval, D.; Palmer, L. I.; Read de Alaniz, J. *Chem. Sci.* **2013**, *4*, 3857. (c) Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14472.

(3) For initial copper-catalyzed aerobic oxidation protocols, see: (a) Chaiyaveij, D.; Cleary, L.; Batsanov, A. S.; Marder, T. B.; Shea, K. J.; Whiting, A. *Org. Lett.* **2011**, *13*, 3442−5. (b) Frazier, C. P.; Engelking, J. R.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2011**, *133*, 10430.

(4) For selected reviews, see: (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234. (b) Palmer, L. I.; Frazier, C. P.; Read de Alaniz, J. *Synthesis* **2013**, *46*, 269. (c) Yu, C.; Song, A.; Zhang, F. *ChemCatChem* **2014**, *6*, 1863.

(5) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, *2004*, 1377.

(6) For select reviews, see: (a) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (b) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131. (c) Iwasa, S.; Fakhruddin, A.; Nishiyama, H. *Mini-Rev. Org. Chem.* **2005**, *2*, 157. (d) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514. (e) Baidya, M.; Yamamoto, H. *Synthesis* **2013**, *45*, 1931.

(7) For asymmetric examples of nitroso ene reactions, see: (a) Braun, H.; Felber, H.; Kreße, G.; Ritter, A.; Schmidtchen, F. P.; Schneider, A. *Tetrahedron* **1991**, *47*, 3313. (b) Adam, W.; Degen, H.-G.; Krebs, O.; Saha-Möller, C. R. *J. Am. Chem. Soc.* **2002**, *124*, 12938. (c) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3249. (d) Yang, B.; Miller, M. J. *Tetrahedron Lett.* **2010**, *51*, 328. (e) Atkinson, D.; Kabeshov, M. A.; Edgar, M.; Malkov, A. V. *Adv. Synth. Catal.* **2011**, *353*, 3347. (f) Teo, Y. C.; Pan, Y.; Tan, C. H. *ChemCatChem* **2013**, *5*, 235. (g) Ouyang, J.; Yan, R.; Mi, X.; Hong, R. *Angew. Chem., Int. Ed.* **2015**, DOI: 10.1002/anie.201505251.

(8) For select examples, see: (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (b) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (c) Mikami, K.; Matsukawa, S.; Nagashima, M.; Funabashi, H.; Morishima, H. *Tetrahedron Lett.* **1997**, *38*, 579. (d) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882. (e) Ruck, R. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 4771. (f) Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, *129*, 12950. (g) Honda, K.; Mikami, K. *Asian J. Org. Chem.* **2014**, *3*, 34.

(9) For select examples, see: (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (b) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (c) Zhao, C.; Mitchell, T. A.; Vallakati, R.; Pérez, L. M.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 3084. (d) Matsuo, J.-i.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9109.

(10) For related work that was reported while our manuscript was under preparation, see: Ramakrishna, I.; Grandhi, G. S.; Sahoo, H.; Baidya, M. *Chem. Commun.* **2015**, DOI: 10.1039/C5CC05459A.

(11) (a) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Chem. Lett.* **1983**, *12*, 863. (b) Sasaki, T.; Mori, K.; Ohno, M. *Synthesis* **1985**, *1985*, 280. (c) Ohno, M.; Mori, K.; Ido, M.; Eguchi, S. *Synthesis* **1986**, *1986*, 666. (d) Ohno, M.; Ido, M.; Eguchi, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1530. (e) Ohno, M.; Ido, M.; Shimizu, S.; Eguchi, S. *Synthesis* **1990**, *1990*, 703.

(12) Kawasaki, M.; Li, P.; Yamamoto, H. *Angew. Chem.* **2008**, *120*, 3855.

(13) For recent asymmetric α-amination of nonactivated carbonyls, see: (a) Miles, D. H.; Guasch, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 7632. (b) Yang, X.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3205.

(14) For select examples, see: (a) Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791. (b) Adam, W.; Bottke, N.; Krebs, O. *Org. Lett.* **2000**, *2*, 3293. (c) Adam, W.; Bottke, N.; Engels, B.; Krebs, O. *J. Am. Chem. Soc.* **2001**, *123*, 5542. (d) Adam, W.; Krebs, O.; Orfanopoulos, M.; Stratakis, M. *J. Org. Chem.* **2002**, *67*, 8395. (e) Leach, A. G.; Houk, K. N. *Org. Biomol. Chem.* **2003**, *1*, 1389.

(15) For use of Oppolzer's sultam in nitrosocarbonyl reactions, see: (a) Gouverneur, V.; Dive, G.; Ghosez, L. *Tetrahedron: Asymmetry* **1991**, *2*, 1173. (b) Chapuis, C.; Laumer, J.-Y. D. S.; Marty, M. *Helv. Chim. Acta* **1997**, *80*, 146. (c) Gouverneur, V.; McCarthy, S. J.; Mineur, C.; Belotti, D.; Dive, G.; Ghosez, L. *Tetrahedron* **1998**, *54*, 10537. (d) Cabanal-Duvillard, I.; Berrien, J.-F.; Ghosez, L.; Husson, H.-P.; Royer, J. *Tetrahedron* **2000**, *56*, 3763. (e) Frazier, C. P.; Bugarin, A.; Engelking, J. R.; Read de Alaniz, J. *Org. Lett.* **2012**, *14*, 3620.

(16) Both antipodes of compound **2** are commerically available; see the Supportion Information for Sigma-Aldrich catalog numbers.

(17) Silyl ketene acetals derived from oxo-esters were prone to hydrolysis under the reaction conditions.

(18) (a) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (b) Fujiwara, S.; Kambe, N. In *Chalcogenocarboxylic Acid Derivatives*; Kato, S., Ed.; Springer: Berlin, 2005; Vol. *251*, pp 87−140. (c) Ogawa, K. A.; Boydston, A. J. *Org. Lett.* **2014**, *16*, 1928.

(19) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650.

(20) The product derived from (*Z*)-Silyl ketene thioacetal of **25** was isolated as a racemate.

(21) Note that the *E*/*Z* assignment to silyl ketene thioacetals is opposite that of silyl enol ethers due to the higher priority given to sulfur.

(22) Ottenheijm, H. C. J.; Herscheid, J. D. M. *Chem. Rev.* **1986**, *86*, 697.

(23) (a) Grundke, G.; Keese, W.; Rimpler, M. *Synthesis* **1987**, *1987*, 1115. (b) Di Gioia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Siciliano, C. *J. Org. Chem.* **2005**, *70*, 10494.

(24) Zhang, X.; Xie, W.; Qu, S.; Pan, T.; Wang, X.; Le, W. *Biochem. Biophys. Res. Commun.* **2005**, *333*, 544.

(25) (a) Butler, A.; Theisen, R. M. *Coord. Chem. Rev.* **2010**, *254*, 288. (b) Zane, H. K.; Butler, A. *J. Nat. Prod.* **2013**, *76*, 648. (c) Kem, M. P.; Zane, H. K.; Springer, S. D.; Gauglitz, J. M.; Butler, A. *Metallomics* **2014**, *6*, 1150.

(26) For select examples, see: (a) Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 3864. (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.

(27) Fontana, F.; Chen, C. C.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3454.

(28) Shinabarger, D. *Expert Opin. Invest. Drugs* **1999**, *8*, 1195.

(29) Guy, M.; Freeman, S.; Alder, J.; Brandt, S. *Cent. Eur. J. Chem.* **2008**, *6*, 526.

DOI: 10.1021/acs.orglett.5b02208
Org. Lett. 2015, 17, 4514−4517