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[3 + 1]- and [3 + 2]-Cycloadditions of Azaoxyallyl Cations and Sulfur Ylides

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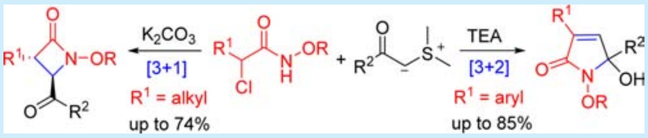
S Supporting Information

ABSTRACT: A new formal [3 + 1]-cycloaddition reaction of azaoxyallyl cation intermediates, generated in situ from α-halo hydroxamates bearing α-alkyl groups, and sulfur ylides is reported, furnishing useful β-lactams (dr >19:1) in fair to modest yields. In contrast, an unexpected formal [3 + 2]-cycloaddition reaction occurs to give γ-lactam derivatives for α-halo hydroxamates with α-aryl groups and sulfur ylides in the presence of bases.



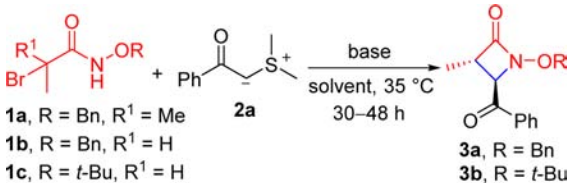
As a type of valuable and powerful reagents, sulfur ylides have been widely utilized as one-carbon units in [2 + 1]-cycloadditions to build epoxides,[1] aziridines,[2] and cyclopropanes[3] or in [4 + 1]-cycloadditions to construct indolines,[4] oxazolidin-2-ones,[5] pyrrolines,[6] and other useful compounds.[7] They have been occasionally applied in [3 + 3]-cycloaddition reactions to access 4*H*-pyrans[8] and cyclohexadiene derivatives.[9] In addition, chemists also use sulfur ylides in some cascade reactions to produce complex cyclic compounds.[9,10] Nevertheless, the development of new cycloaddition patterns of these zwitterionic substances to furnish more ring systems still remains to be expanded.

On the other hand, azaoxyallyl cation intermediates, which can be readily generated from α-halo hydroxamates in the presence of bases, were recently used as versatile 3-units in [3 + 4]- and [3 + 2]-cycloaddition reactions with electron-rich dienes[11] and indoles,[12] respectively. Consequently, we postulated that the azaoxyallyl cations might have high potential for assembly with sulfur ylides in an unprecedented [3 + 1]-cycloaddition manner,[13] as proposed in Scheme 1, providing a convenient protocol to β-lactams,[14] which are key skeletons in a variety of biologically active compounds used against bacterial infections[15] and other types of diseases such as antifungal,[16] anticancer,[17] and antiviral.[18]

The initial reaction of α-bromo hydroxamate **1a** and sulfur ylide **2a** resulted in no success in the presence of excess K_2CO_3, and only the HBr elimination product of **1a** was observed (Table 1, entry 1). Fortunately, by using substrate **1b** as the

Scheme 1. [3 + 1]-Cycloadditions of Azaoxyallyl Cations and Sulfur Ylides

Table 1. Screening Studies of [3 + 1]-Cycloadditions of α-Bromo Hydroxamates 1 and Sulfur Ylide 2a[a]



entry	1	solvent	base	3 (yield,[b] %)
1	**1a**	CH_2Cl_2	K_2CO_3	
2	**1b**	CH_2Cl_2	K_2CO_3	**3a** (41)
3[c]	**1b**	CH_2Cl_2	K_2CO_3	**3a** (23)
4	**1b**	CH_2Cl_2	Na_2CO_3	**3a** (31)
5	**1b**	CH_2Cl_2	K_2HPO_4	**3a** (40)
6	**1b**	CH_2Cl_2	DIPEA	**3a** (39)
7[d]	**1b**	CH_2Cl_2	K_2CO_3	**3a** (40)
8	**1b**	MeCN	K_2CO_3	**3a** (39)
9	**1b**	THF	K_2CO_3	**3a** (39)
10	**1b**	toluene	K_2CO_3	**3a** (36)
11[e]	**1b**	CH_2Cl_2/HFIP	K_2CO_3	**3a** (/)
12[f]	**1b**	CH_2Cl_2	K_2CO_3	**3a** (28)
13[g]	**1b**	CH_2Cl_2	K_2CO_3	**3a** (47)
14[g]	**1c**	CH_2Cl_2	K_2CO_3	**3b** [79 (74)][h]

[a]Unless noted otherwise, reactions were performed with **1** (0.1 mmol), **2a** (0.05 mmol), and base (0.2 mmol) in solvent (0.5 mL) at 35 °C for 30–48 h. [b]Determined by crude ^1H NMR analysis using mesitylene as the internal standard. [c]0.05 mmol of **1b** was used. [d]With 0.1 mmol of base. [e]HFIP/CH_2Cl_2 = 1:1. [f]At 0 °C. [g]1 mL of CH_2Cl_2 was used. [h]Values in parentheses refer to the isolated yield.

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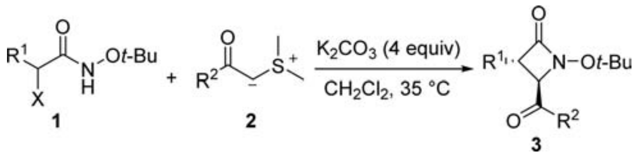
precursor, the desired [3 + 1] β-lactam product **3a** was detected in a fair yield but with excellent diastereoselectivity (Table 1, entry 2). The yield was diminished when lower amounts of **1b** were used (Table 1, entry 3). Other inorganic or organic bases or less K_2CO_3 were tested, and the similar yields were obtained (Table 1, entries 4−7). In addition, slightly inferior yields were also produced in other solvents (Table 1, entries 8−10), but the reaction was prohibited by adding some hexafluoro-2-propanol (HFIP) (Table 1, entry 11).[11,12] The yield was decreased at lower temperature even after a longer time (Table 1, entry 12). The reaction could be improved in a diluted solution (Table 1, entry 13). To our gratification, the yield of product **3b** was significantly increased by utilizing *O-tert*-butyl substrate **1c** owing to fewer side reactions (Table 1, entry 14).

Consequently, the substrate scope and limitations of α-halo hydroxamates and sulfur ylides were explored under the optimized reaction conditions. The results are summarized in Table 2. At first, a variety of sulfur yields **2** were investigated in the combination with α-bromo hydroxamate **1c**. Moderate yields were obtained for ylides with electron-donating aryl or 2-naphthyl groups (Table 2, entries 2−4), but only low to fair yields could be produced for those with electron-withdrawing aryl or 2-thienyl groups (Table 2, entries 5−8). Unfortunately, sulfur ylides with either an acetyl or an ester group failed to provide the desired β-lactam products (Table 2, entries 9 and 10). On the other hand, α-bromo hydroxamates with larger α-alkyl groups were compatible substrates, though low to modest yields were generally attained (Table 2, entries 11−14).

Table 2. Substrate Scope and Limitations of [3 + 1]-Cycloadditions[a]

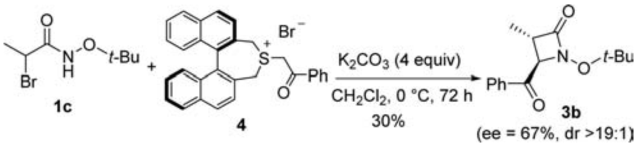


entry	X	R^1	R^2	time (h)	**3** (yield,[b] %)
1	Br	Me	Ph	30	**3b** (74)
2	Br	Me	4-MeC_6H_4	24	**3c** (55)
3	Br	Me	3-MeOC_6H_4	30	**3d** (74)
4	Br	Me	2-naphthyl	24	**3e** (68)
5	Br	Me	3-ClC_6H_4	30	**3f** (47)
6	Br	Me	4-BrC_6H_4	25	**3g** (29)
7	Br	Me	$4\text{-CF}_3C_6H_4$	24	**3h** (25)
8	Br	Me	2-thienyl	24	**3i** (30)
9	Br	Me	Me	48	
10	Br	Me	OEt	48	
11	Cl	Et	Ph	28	**3j** (53)
12	Cl	*n*-Pr	Ph	30	**3k** (56)
13	Cl	$Ph(CH_2)_2$−	Ph	30	**3l** (47)
14	Cl	*i*-Pr	Ph	30	**3m** (25)

[a] Unless noted otherwise, reactions were performed with **1** (0.4 mmol) and **2** (0.2 mmol), K_2CO_3 (0.8 mmol) in CH_2Cl_2 (4.0 mL) at 35 °C. [b] Yield of the isolated product.

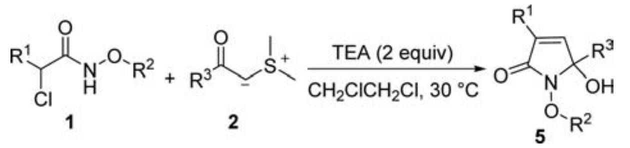
We also investigated the potential asymmetric [3 + 1]-cycloaddition reaction by employing a chiral sulfur ylide substrate. Unfortunately, much lower reactivity was generally observed, and **3b** was obtained with a moderate ee value from **1c** and sulfur ylide precursor **4** at 0 °C (Scheme 2).[19]

Scheme 2. Attempt in Asymmetric [3 + 1]-Cycloaddition



Interestingly, a different [3 + 2]-cycloaddition reaction occurred between α-chloro hydroxamate **1d** with an α-phenyl group and sulfur ylide **2a**, furnishing a γ-lactam product **5a** with a hemiaminal moiety. Further reaction condition screenings indicated that a high yield could be obtained in 1,2-dichloroethane (DCE) at 30 °C, using TEA as the base (Table 3, entry 1). Subsequently, the substrate scope and limitations of the new [3 + 2]-cycloaddition reaction were explored. As summarized in Table 3, α-chloro hydroxamates bearing a variety of aryl or 3-thienyl groups could be well tolerated under the optimized conditions, smoothly producing the corresponding γ-lactam derivatives **5b**−**i** in moderate to good yields (Table 3, entries 2−9). On the other hand, sulfur ylides with various aryl, heteroaryl, or even 2-styryl groups were investigated, and comparable yields were generally obtained (Table 3, entries 10−18). It was notable that sulfonium salts with diversely structured alkyl groups could be directly utilized, though the corresponding products **5s**−**u** were delivered in low to fair yields (Table 3, entries 19−21). In addition, α-chloro

Table 3. Unexpected [3 + 2]-Cycloadditions of α-Chloro Hydroxamates 1 with α-Aryl Groups and Sulfur Ylides 2[a]



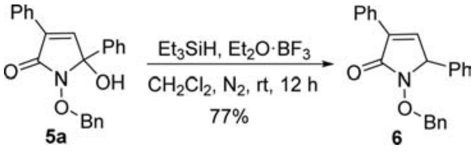
entry	R^1	R^3	time (h)	**5** (yield,[b] %)
1	Ph	Ph	15	**5a** (85)
2	3-MeC_6H_4	Ph	19	**5b** (80)
3	4-MeC_6H_4	Ph	18	**5c** (67)
4	2-MeOC_6H_4	Ph	16	**5d** (65)
5	2-FC_6H_4	Ph	16	**5e** (80)
6	4-ClC_6H_4	Ph	18	**5f** (77)
7	3-BrC_6H_4	Ph	18	**5g** (69)
8	1-naphthyl	Ph	17	**5h** (73)
9	3-thienyl	Ph	16	**5i** (66)
10	Ph	4-MeC_6H_4	16	**5j** (62)
11	Ph	$2,4\text{-Me}_2C_6H_3$	17	**5k** (52)
12	Ph	3-MeOC_6H_4	16	**5l** (78)
13	Ph	2-ClC_6H_4	17	**5m** (53)
14	Ph	3-ClC_6H_4	16	**5n** (79)
15	Ph	4-BrC_6H_4	16	**5o** (65)
16	Ph	2-naphthyl	20	**5p** (65)
17	Ph	2-thienyl	20	**5q** (62)
18	Ph	2-styryl	16	**5r** (52)
19[c]	Ph	Me	18	**5s** (42)
20[c]	Ph	cyclopropyl	24	**5t** (26)
21[c]	Ph	*t*-Bu	24	**5u** (27)
22[d]	Ph	Ph	16	**5v** (80)
23[e]	Ph	Ph	18	**5w** (72)

[a] Unless noted otherwise, reactions were performed with **1** (0.4 mmol, R^2 = Bn), **2** (0.2 mmol), TEA (0.4 mmol) in CH_2ClCH_2Cl (2.0 mL) at 30 °C. [b] Yield of the isolated product. [c] Sulfonium salt and TEA (0.6 mmol) were used. [d] R^2 = Et. [e] R^2 = Ph_2CH-.

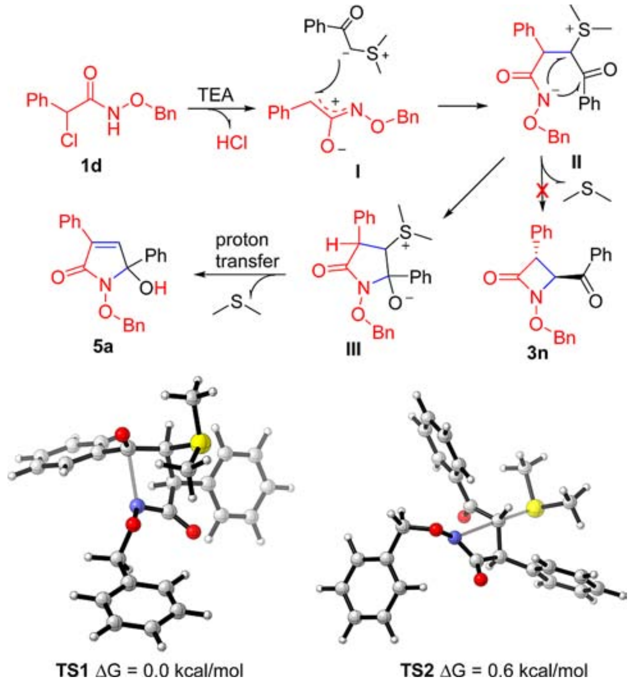
hydroxamates with other *O*-alkyl groups were also studied, and good yields were attained (Table 3, entries 22 and 23).

The hydroxyl group of product **5a** could be easily removed in the presence of Et_3SiH and $BF_3{\cdot}Et_2O$ under N_2,[20] giving a 1,5-dihydro-2*H*-pyrrol-2-one derivative **6** in a good yield (Scheme 3).

Scheme 3. Dehydroxylation of [3 + 2] Product 5a



Scheme 4. Proposed Mechanism for the Formation of 5a and DFT Computational Calculation Study



TS1 ΔG = 0.0 kcal/mol **TS2** ΔG = 0.6 kcal/mol

As outlined in Scheme 4, a plausible reaction mechanism to generate the *γ*-lactam product was proposed. The sulfur ylide **2a** reacts with the in situ formed azaoxyallyl cation **I**, delivering the zwitterionic intermediate **II**. The nitrogen anion does not substitute the sulfonium to give *β*-lactam **3n** probably due to steric hindrance, but attacks the carbonyl group to produce intermediate **III**.[21] Finally, proton transfer followed by elimination of dimethyl sulfide affords the observed *γ*-lactam product **5a** with a hemiaminal functionality. Moreover, brief density functional theory (DFT) calculations were performed to clarify the regioselective cycloadditions. The key transition states **TS1** and **TS2** for the formation of intermediate **III** and **3n**, respectively, were calculated, as shown in Scheme 4. The Gibbs free energy of **TS1** is 0.6 kcal/mol lower than that of **TS2**, suggesting that the five-membered ring system would be theoretically more favorable, which is consistent with the experimental results.

In conclusion, we have investigated the cycloaddition reactions of azaoxyallyl cations generated in situ from *α*-halo hydroxamates and sulfur ylides. A formal [3 + 1]-cycloaddition reaction was observed for *α*-halo hydroxamates bearing *α*-alkyl groups and *β*-lactams derivatives were obtained in fair to modest yields with excellent diastereoselectivity (dr >19:1), while moderate enantioselectivity was realized by employing chiral sulfur ylides. In contrast, for *α*-halo hydroxamates with *α*-aryl groups, an interesting formal [3 + 2]-cycloaddition reaction occurred to give *γ*-lactam derivatives in which sulfur ylides with ketone groups performed as previously unreported two-carbon partners. Additional results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01194.

Complete experimental procedures and characterization of new products (PDF)
X-ray data for **3a** (CCDC 1474806) (CIF)
X-ray data for **5a** (CCDC 1474807) (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Aggarwal, V. K. W.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611. (b) Illa, O.; Arshad, M.; Ros, A.; McGarrigle, E. M.; Aggarwal, V. K. W. *J. Am. Chem. Soc.* **2010**, *132*, 1828. (c) Miyake, Y.; Oyamada, A.; Nishibayashi, Y.; Uemura, S. *Heteroat. Chem.* **2002**, *13*, 270. (d) Aggarwal, V. K. W.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105. (e) Aggarwal, V. K.; Ford, J. G.; Fonquerna, S.; Adams, H.; Jones, R. V. H.; Fieldhouse, R. *J. Am. Chem. Soc.* **1998**, *120*, 8328. (f) Wu, H.-Y.; Chang, C.-W.; Chein, R.-J. *J. Org. Chem.* **2013**, *78*, 5788.

(2) (a) Illa, O.; Namutebi, M.; Saha, C.; Ostovar, M.; Chen, C. C.; Haddow, M. F.; Nocquet-Thibault, S.; Lusi, M.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 11951. (b) Marsini, M. A.; Reeves, J. T.; Desrosiers, J. N.; Herbage, M. A.; Savoie, J.; Li, Z.; Fandrick, K. R.; Sader, C. A.; McKibben, B.; Gao, D.-A.; Cui, J.; Gonnella, N. C.; Lee, H.; Wei, X.; Roschangar, F.; Lu, B.-Z.; Senanayake, C. H. *Org. Lett.* **2015**, *17*, 5614. (c) Janardanan, D.; Sunoj, R. B. *J. Org. Chem.* **2008**, *73*, 8163. (d) Aggarwal, V. K.; Vasse, J.-L. *Org. Lett.* **2003**, *5*, 3987. (e) Zhu, B.-H.; Zheng, J.-C.; Yu, C.-B.; Sun, X.-L.; Zhou, Y.-G.; Shen, Q.; Tang, Y. *Org. Lett.* **2010**, *12*, 504.

(3) (a) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (b) Yuan, Z.; Fang, X.; Li, X.; Wu, J.; Yao, H.; Lin, A. *J. Org. Chem.* **2015**, *80*, 11123. (c) Deng, X.-M.; Cai, P.; Ye, S.; Sun, X.-L.; Liao, W.-W.; Li, K.; Tang, Y.; Wu, Y.-D.; Dai, L.-X. *J. Am. Chem. Soc.* **2006**, *128*, 9730. (d) Ye, S.; Huang, Z.-Z.; Xia, C.-A.; Tang, Y.; Dai, L.-X. *J. Am. Chem. Soc.* **2002**, *124*, 2432. (e) Zhang, X.-Z.; Du, J.-Y.; Deng, Y.-H.; Chu, W.-D.; Yan, X.; Yu, K.-Y.; Fan, C.-A. *J. Org. Chem.* **2016**, *81*, 2598.

(4) (a) Yang, Q.-Q.; Wang, Q.; An, J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem. - Eur. J.* **2013**, *19*, 8401. (b) Wang, Q.; Qi, X.; Lu, L.-Q.; Li, T.-R.; Yuan, Z.-G.; Zhang, K.; Li, B.-J.; Lan, Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2016**, *55*, 2840.

(5) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946.

(6) Lu, L.-Q.; Zhang, J.-J.; Li, F.; Cheng, Y.; An, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4495.

(7) (a) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924. (b) Xie, P.; Wang, L.; Yang, L.; Li, E.; Ma, J.; Huang, Y.; Chen, R. *J. Org. Chem.* **2011**, *76*, 7699.

(8) Li, K.; Hu, J.; Liu, H.; Tong, X. *Chem. Commun.* **2012**, *48*, 2900.

(9) Wang, Q.-G.; Deng, X.-M.; Zhu, B.-H.; Ye, L.-W.; Sun, X.-L.; Li, C.-Y.; Zhu, C.-Y.; Shen, Q.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408.

(10) Lu, L.-Q.; Li, F.; An, J.; Zhang, J.-J.; An, X.-L.; Hua, Q.-L.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9542.

(11) Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc.* **2011**, *133*, 7688.

(12) (a) Acharya, A.; Anumandla, D.; Jeffrey, C. S. *J. Am. Chem. Soc.* **2015**, *137*, 14858. (b) DiPoto, M. C.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14861.

(13) For limited examples of [3 + 1]-cycloadditions to access diverse four-membered ring systems, see: (a) Barluenga, J.; Riesgo, L.; Lonzi, G.; Tomás, M.; López, L. A. *Chem. - Eur. J.* **2012**, *18*, 9221. (b) Xiong, Y.; Yao, S.; Driess, M. *Organometallics* **2010**, *29*, 987. (c) Schwarz, D. E.; Rauchfuss, T. B. *Chem. Commun.* **2000**, 1123. (d) May, A.; Roesky, H. W.; Herbst-Irmer, R.; Freitag, S.; Sheldrick, G. M. *Organometallics* **1992**, *11*, 15. (e) Burger, K.; Marschke, G.; Manz, F. *J. Heterocycl. Chem.* **1982**, *19*, 1315.

(14) For a comprehensive review of β-lactams, see: Pitts, C. R.; Lectka, T. *Chem. Rev.* **2014**, *114*, 7930.

(15) Roberts, J. A.; Webb, S.; Paterson, D.; Ho, K. M.; Lipman, J. *Crit. Care Med.* **2009**, *37*, 2071.

(16) (a) Vatmurge, N. S.; Hazra, B. G.; Pore, V. S.; Shirazi, F.; Chavan, P. S.; Deshpande, M. V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2043. (b) O'Driscoll, M.; Greenhalgh, K.; Young, A.; Turos, E.; Dickey, S.; Lim, D. V. *Bioorg. Med. Chem.* **2008**, *16*, 7832.

(17) (a) Singh, P.; Raj, R.; Kumar, V.; Mahajan, M. P.; Bedi, P. M.; Kaur, T.; Saxena, A. K. *Eur. J. Med. Chem.* **2012**, *47*, 594. (b) Banik, B. K.; Becker, F. F.; Banik, I. *Bioorg. Med. Chem.* **2004**, *12*, 2523.

(18) (a) Gerona-Navarro, G.; Pérez de Vega, M. J.; García-López, M. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J.; González-Muñiz, R. *J. Med. Chem.* **2005**, *48*, 2612. (b) D'hooghe, M.; Mollet, K.; De Vreese, R.; Jonckers, T. H. M.; Dams, G.; De Kimpe, N. *J. Med. Chem.* **2012**, *55*, 5637.

(19) The absolute configuration of chiral **3b** has not been assigned yet.

(20) Ruan, Y.-P.; Chen, M.-D.; He, M.-Z.; Zhou, X.; Huang, P.-Q. *Synth. Commun.* **2004**, *34*, 853.

(21) The N−O functionality would enhance nucleophilicity at the nitrogen center via the α-effect, see: Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.

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