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Ru-Catalyzed Rearrangement of *N*-Methyl Isoxazolidines to *N*−H 1,3-Oxazinanes: A Strategy of Self-Hydride Transferring Cleavage of N−O Bonds

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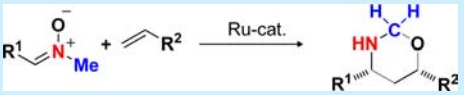
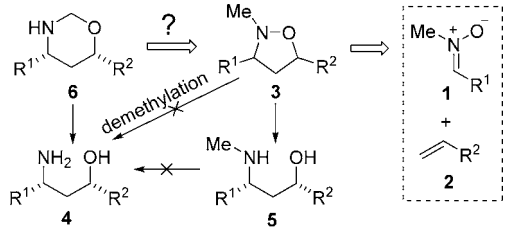
Supporting Information

ABSTRACT: A strategy of ruthenium-catalyzed self-hydride transferring cleavage of N−O bonds was designed and utilized in a cascade 1,3-dipolar cyclization of alkenes and *N*-methyl nitrones followed by an *N*-demethylative rearrangement, furnishing synthetically useful *N*−H 1,3-oxazinanes.



The dipolar cycloaddition of nitrones **1** with alkenes **2** has already been well-established as a powerful method for the construction of *N*-alkyl isoxazolidines[1] **3** which could be further converted to the corresponding *N*-alkyl 1,3-aminoalcohols through the reductive cleavage of N−O bonds, but the subsequent removal of the *N*-alkyl group is difficult (Scheme 1). However, six-membered 1,3-oxazinanes[2] **6** are useful

Scheme 1. Possible Routes from *N*-Methyl Isoxazolidines to *N*−H 1,3-Oxazinanes



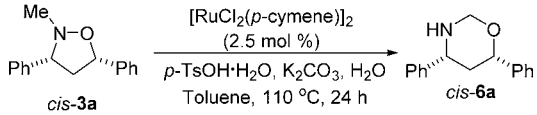
synthetic building blocks which can be readily converted to *N*-alkyl- or *N*−H-functionalized 1,3-aminoalcohols in one step. Thus, the transformation of isoxazolidines **3** to 1,3-oxazinanes **6** would be synthetically useful, but remains rare.[3,4] The development of a generally applicable transformation of isoxazolidines **3** to *N*−H 1,3-oxazinanes **6** remains to be established.

Here we report our efforts toward the development of a reaction cascade from *N*-methyl nitrones to *N*−H 1,3-oxazinanes through novel Ru-catalyzed[5] self-hydride transferring cleavage of N−O bonds.

cis-Isoxazolidine **3a** ($R^1 = R^2 = Ph$) was initially tested with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst to probe the possibility of N−O cleavage followed by a C−H oxidative cleavage *N*-demethylation reaction. It was found that *cis*-**3a** was stereospecifically converted to the desired *cis*-**6a** in quantitative conversion (Scheme 2).

Since *cis*-isoxazolidine *cis*-**3a** could be prepared as the major product in situ by the 1,3-dipolar cycloaddition reaction of nitrone **1a** (R^1 = Ph) and styrene at 110 °C, we investigated the

Scheme 2. Conversion of *cis*-3a to *cis*-6a



cascade formation of **6a** from **1a** and styrene in the presence of various precatalysts such as $Pd(OAc)_2$, $Co(OAc)_2$, $BF_3{\cdot}Et_2O$, $AlCl_3$, $Fe(OTf)_2$, $RuCl_3{\cdot}xH_2O$, $IrCl_3{\cdot}xH_2O$, $RhCl_3{\cdot}xH_2O$, $RuCl_2(PPh_3)_3$, and $[RuCl_2(p\text{-cymene})]_2$ (see Supporting Information (SI) for details). Only $[RuCl_2(p\text{-cymene})]_2$ and $RuCl_2(PPh_3)_3$ were found to be catalytically active for the desired transformation (Table 1, entries 1, 14−16). Further investigation revealed that K_2CO_3 and *p*-TsOH·H_2O (PTSA) facilitate higher conversions (Table 1, entries 1 and 7), as does the presence of water (Table 1, entries 1 and 4). It is likely that this is in part due to the increased solubility of inorganic salts in toluene. In the absence of Ru or other additives (*p*-TsOH·H_2O−K_2CO_3−H_2O) the reaction did not proceed (Table 1, entries 6 and 7). $[RuCl_2(p\text{-cymene})]_2$ alone has an inhibiting effect on the first cycloaddition reaction because of decomposition of nitrone to benzaldehyde (Table 1, entry 7). Neither PTSA nor K_2CO_3 was found to catalyze the reaction (Table 1, entries 8 and 9). Substituting PTSA and K_2CO_3 by other carboxylic salts resulted in lower conversions (Table 1, entries 10−11). Using other sulfonic acids such as CSA and methanesulfonic acid also resulted in low conversions (Table 1, entries 12−13). In most cases *trans*-**3a** was partially recovered. The treatment of *trans*-**3a** under standard conditions gave rise to partial decomposition of starting material instead of formation of *trans*-**6a**. *N*-Ethyl and *N*-benzyl phenyl nitrones were also tested, but only 24% and 2% conversions were achieved (not shown in the table).

The reversibility of the cycloaddition reaction between nitrone and styrene was also investigated to probe whether

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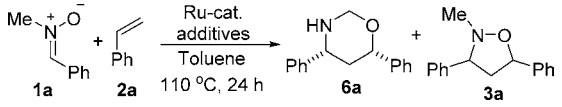
Table 1. Investigation of the Reaction Conditions

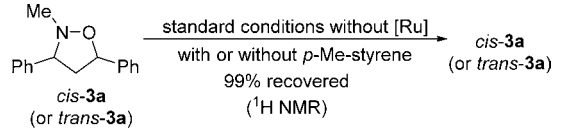


entry	cat.	additives	*t*-3a/*c*-3a/6a, conv (%)[b]
1[a]	[Ru]	K_2CO_3/PTSA/H_2O	5/0/60[c]
2	[Ru]	PTSA/H_2O	14/12/4
3	[Ru]	K_2CO_3/H_2O	24/15/41
4	[Ru]	K_2CO_3/PTSA	27/18/39
5	[Ru]	K_2CO_3/PTSA/4 Å MS	4/3/49
6	–	K_2CO_3/PTSA/H_2O	20/84/0
7	[Ru]	–	24/38/2[d]
8	–	PTSA	40/50/0
9	–	K_2CO_3/H_2O	20/83/0
10	[Ru]	HCO_2Na	21/10/21
11	[Ru]	K_2CO_3/H_2O/2,4,6-$Me_3C_6H_2CO_2H$	20/22/23
12[e]	[Ru]	K_2CO_3/H_2O/CSA	20/40/9
13	[Ru]	K_2CO_3/H_2O/$MeSO_3H$	25/50/17
14	$RuCl_2(PPh_3)_3$	K_2CO_3/PTSA/H_2O	13/0/35
15	$RhCl_3{\cdot}xH_2O$	K_2CO_3/PTSA/H_2O	19/84/0
16	$IrCl_3{\cdot}xH_2O$	K_2CO_3/PTSA/H_2O	15/79/0

[a]Standard conditions: 0.5 mmol of **1a**, 2.0 mmol of styrene, 2.5 mol % $[RuCl_2(p\text{-cymene})]_2$ [Ru], 15 mol % *p*-TsOH·H_2O (PTSA), 1.0 mmol of H_2O, 0.5 mmol of K_2CO_3, 2.0 mL of toluene, 110 °C, 24 h. [b]Conversions of *trans*-**3a**, *cis*-**3a**, and **6a** were determined by ^{1}H NMR (400 MHz) using CH_3NO_2 and ^{t}BuOMe as internal standards. [c]Styrene was recovered in 80% yield. [d]23% PhCHO and 71% styrene were observed. [e]CSA refers to (+)-Camphor-10-sulfonic acid.

trans-**3a** could isomerize to *cis*-**3a**, which contributed to higher yields of 1,3-oxazinane adducts. The starting materials were recovered, in both the presence and absence of *p*-Me-styrene (Scheme 3). This suggests that the 1,3-dipolar cycloaddition

Scheme 3. Probing the *cis*/*trans* Isomerization of 3a

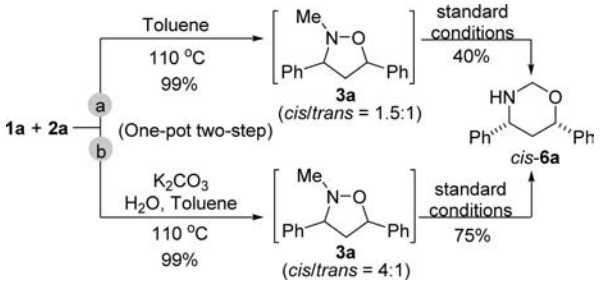


reaction of nitrone **3a** with styrene is not reversible for either the *cis*- or *trans*-isomers of product **3a**. Since the isomerizations of *cis*- and *trans*-isoxazolidines were not observed and only *cis*-**3a** could be converted to *cis*-**6a** (Scheme 2), the conversions to the desired *N*−H 1,3-oxazinanes are likely dependent on the *cis*/*trans* ratios of the isoxazolidine intermediates.

The [3 + 2] cycloaddition between **1a** and styrene without a catalyst or additives produced *cis*- and *trans*-**3a** in a 1.5:1 ratio (Scheme 4). Surprisingly, the *cis*/*trans* ratio increased to 4:1 when K_2CO_3 and H_2O were added. A modified one-pot two-step version of this Ru-catalyzed cascade reaction between **1a** and styrene was performed using K_2CO_3 and H_2O as additives for the first [3 + 2] cycloaddition step, resulting in an overall 75% yield of *cis*-**6a**. This yield is higher than that of the one-pot reaction reported in Table 1 entry 1, suggesting that the two-step cascade process improves the *cis*/*trans*-selectivity, resulting in a higher yield of the target 1,3-oxazinane product.

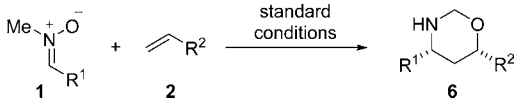
Under standard conditions, the sensitivity of the reaction to both functionalized nitrone and styrene starting materials was

Scheme 4. Effect of Additives



investigated. First, various nitrones were subjected to standard conditions with styrene, resulting in acceptable yields of the *cis*-isomer (Table 2, entries 1−8). Naphthyl and 2-furyl nitrones

Table 2. Scope of the Reaction[a]



entry	R^1, 1	R^2, 2	6	yield (%)[b]
1	Ph, **1a**	Ph, **2a**	**6a**	68
2	Ph, **1a**	Ph, **2a**	**6a**	82[c]
3	1-Naph, **1b**	Ph, **2a**	**6b**	60
4	2-Furyl, **1c**	Ph, **2a**	**6c**	60
5	3-ClC_6H_4, **1d**	Ph, **2a**	**6d**	60
6	2-BrC_6H_4, **1e**	Ph, **2a**	**6e**	60
7	4-$CF_3C_6H_4$, **1f**	Ph, **2a**	**6f**	61
8	3,4-$(Cl)_2C_6H_3$, **1g**	Ph, **2a**	**6g**	71
9	3,4-$(Cl)_2C_6H_3$, **1g**	4-MeC_6H_4, **2b**	**6h**	77
10	3,4-$(Cl)_2C_6H_3$, **1g**	4-ClC_6H_4, **2c**	**6i**	63
11	3,4-$(Cl)_2C_6H_3$, **1g**	2-ClC_6H_4, **2d**	**6j**	68
12	3,4-$(Cl)_2C_6H_3$, **1g**	3-ClC_6H_4, **2e**	**6k**	68
13	3,4-$(Cl)_2C_6H_3$, **1g**	4-^{t}BuC_6H_4, **2f**	**6l**	69
14	3,4-$(Cl)_2C_6H_3$, **1g**	4-BrC_6H_4, **2g**	**6m**	61
15	3,4-$(Cl)_2C_6H_3$, **1g**	2-BrC_6H_4, **2h**	**6n**	62
16	3,4-$(Cl)_2C_6H_3$, **1g**	styryl, **2i**	**6o**	62
17	Ph, **1a**	4-MeC_6H_4, **2b**	**6p**	62
18	4-$CF_3C_6H_4$, **1f**	4-MeC_6H_4, **2b**	**6q**	67
19	2-BrC_6H_4, **1e**	4-MeC_6H_4, **2b**	**6r**	66
20	2-BrC_6H_4, **1e**	4-^{t}BuC_6H_4, **2f**	**6s**	58
21	Ph, **1a**	C_6H_{13}, **2j**	**6t**	54
22	C_5H_{11}, **1h**	Ph, **2a**	**6u**	80[c]

[a]Using standard conditions: 0.5 mmol of **1a**, 2.0 mmol of styrene, 2.5 mol % $[RuCl_2(p\text{-cymene})]_2$, 15 mol % *p*-TsOH·$H_2O$, 1.0 mmol of H_2O, 0.5 mmol of K_2CO_3, 2.0 mL of toluene, 110 °C, 24 h (see SI for details). [b]Isolated yields. [c]Isolated *cis*-**3** was used.

gave the corresponding products **6b** and **6c** in 60% yield each. The reaction was found to tolerate chloro-substitution of both the styrene and nitrone resulting in products **6i**−**k**, which could be isolated in moderate yields from 63% to 68%. 4-Methylstyrene afforded the product **6h** with the highest isolated yield (77%) (Table 2, entry 9). *trans*-1-Phenyl-1,3-butadiene gave the corresponding product **6o** in 62% yield. Phenyl, 4-CF_3-phenyl, and 2-Br-phenyl nitrones could be reacted with 4-methylstyrene under standard conditions to give the corresponding 1,3-oxazinanes **6p**−**r** in 62%, 67%, and 66% yields, respectively (Table 2, entries 17−19). The styrenes bearing 4-methyl and 4-*tert*-butyl groups were treated with 2-

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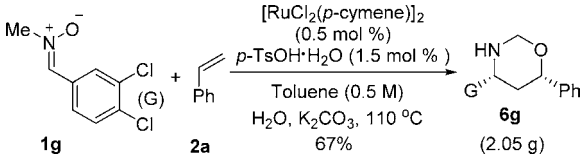
bromophenyl nitrone to give the corresponding products **6r** and **6s** in 66% and 58% yields, respectively.

For the aliphatic alkene, 1-octene, the reaction with phenyl nitrone produced the corresponding cycloproduct **6t** in 54% yield (Table 2, entry 21). The nitrones bearing 2-aliphatic chains were not stable in the presence of K_2CO_3−H_2O under standard conditions, thus the two-step strategy was utilized. For example, the cycloadduct **6u** bearing an *n*-pentyl group was obtained in 80% yield using this method.

The reaction could be scaled up to 1 g each of **1g** and styrene to give 2 g of the corresponding product **6g** in 67% yield. The loading of the Ru-catalyst could be lowered down to 0.5 mol % (Scheme 5).

Scheme 5. Gram-Scale Reaction



The molecular structure of **6m** was determined by an X-ray crystal structure analysis (CCDC 989484) (Figure 1). Configurations of **6a**−**u** were corroborated by the resemblance of NMR analysis.

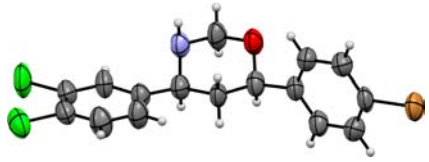
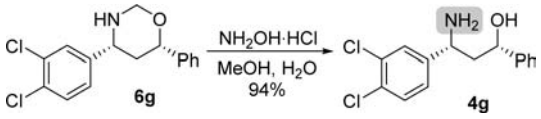


Figure 1. Molecular structure of **6m**, determined by X-ray diffraction (50% probability ellipsoids) (CH_2Cl_2−AcOEt).

Since 1,3-oxazinanes are useful bioactive compounds and synthetic intermediates,[6] we aimed to use them to prepare *syn*-1,3-aminoalcohols (Scheme 6). *cis*-1,3-Oxazinane **6g** was

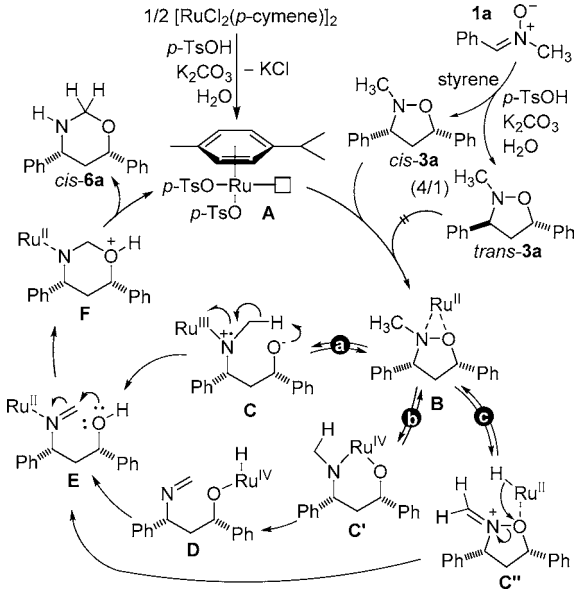
Scheme 6. Transform 6g to 4g



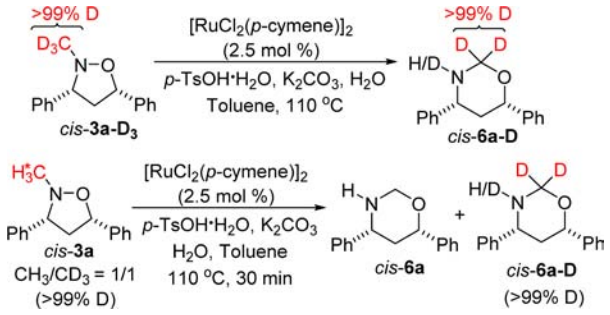
treated with NH_2OH·HCl in wet methanol,[4a,7] and the corresponding *N*−H *syn*-1,3-aminoalcohol **4g** was isolated in 94% yield. Thus, *N*−H 1,3-aminoalcohols could be obtained in excellent yields in a single step.

The proposed reaction mechanism is demonstrated in Scheme 7. Geometric effects and the steric hindrance have a dramatic influence on this reaction that neither *trans*-**3a** nor *N*-ethyl or *N*-benzyl *cis*-**3** could be well converted. To understand the mechanism, deuterium labeling experiments were done and demonstrated in Scheme 8 (for the details of D-labeling experiments, see SI). Probably only *cis*-**3a** might coordinate to catalytically active species **A** to form complex **B** which is transferred to final product **6a** through the single-electron-transfer (SET) pathway (a), the N−O oxidative insertion pathway (b), or the C−H cleavage hydride transferring N−O cleavage pathway (c), all via the key intermediate **E**. The Ru-

Scheme 7. Proposed Mechanism



Scheme 8. Deuterium-Labelling Experiments



catalyst is regenerated after the proton transfer. When *N*-CD_3 *cis*-**3a-D$_3$** (>99% D) was treated under standard conditions, *cis*-**6a-D** (>99% D) was obtained. The kinetic isotope effect (k_H/k_D = 1) indicates that C−H cleavage step is not the rate-limiting step, which indicates pathway (c) might not be involved in this reaction (Scheme 8). Thus, both pathways (a) and (b) seem reasonable.

In conclusion, we have developed a Ru-catalyzed cascade [3 + 2]-cyclization and rearrangement to *N*−H 1,3-oxazinanes using the strategy of self-hydride transferring cleavage of N−O bonds. This novel protocol provides a facile access to synthetically useful *N*-H 1,3-oxazinanes which could not be otherwise synthesized via the conventional dipolar cycloaddition of readily available inexpensive *N*-methyl nitrones. This strategy demonstrates good tolerance to a range of functional groups. Even the *N*-substitution was limited on the methyl group, but in further transformations the corresponding methylene group (N−CH_2−O) will be removed, which makes the strategy more "atom-economic".[8] The detailed mechanistic study, the asymmetric version, and the synthetic applications of this reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For recent reviews: (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(2) For leading references on the synthesis and the applications of 1,2-oxazinanes from nitrones: (a) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (b) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088. (c) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918. (d) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (e) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139. (f) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023.

(3) For a photochemical and ^{t}BuOK (0.5 equiv) promoted radical process: (a) LeBel, N. A.; Lajiness, T. A.; Ledlie, D. B. *J. Am. Chem. Soc.* **1967**, *89*, 3076. For an iridium catalysis under 60 atm of CO and at 150−170 °C: (b) Khumtaveeporn, K.; Alper, H. *J. Org. Chem.* **1995**, *60*, 8142.

(4) (a) Freeman, D. B.; Holubec, A. A.; Weiss, M. W.; Dixon, J. A.; Kakefuda, A.; Ohtsuka, M.; Inoue, M.; Vaswani, R. G.; Ohki, H.; Doan, B. D.; Reisman, S. E.; Stoltz, B. M.; Day, J. J.; Tao, R. N.; Dieterich, N. A.; Wood, J. L. *Tetrahedron* **2010**, *66*, 6647. (b) Rajković, M. M.; Lorenc, L.; Ivan, O.; Juranić, I. O.; Vitnik, Z. J.; Mihailovic, M. L. *Tetrahedron* **1999**, *55*, 6681. (c) Rajković, M. M.; Lorenc, L.; Petrović, I.; Milovanović, A.; Mihailović, M. L. *Tetrahedron Lett.* **1991**, *32*, 7605.

(5) For the reviews on Ru-catalyzed C−H functionalizations: (a) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744. (b) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (d) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211. For selected references: (e) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877. (f) Geary, L. M.; Glasspoole, B. W.; Kim, M. M.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 3796. (g) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741. (h) McNeill, E.; Du Bois, J. *J. Am. Chem. Soc.* **2010**, *132*, 10202. (i) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (j) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 13684. (k) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (l) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687. (m) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750. (n) Yang, S. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209. (o) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (p) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.

(6) (a) Alali, F. Q.; Tahboub, Y. R.; Ibrahim, E. S.; Qandil, A. M.; Tawaha, K.; Burgess, J. P.; Sy, A.; Nakanishi, Y.; Kroll, D. J.; Oberlies, N. H. *Phytochemistry* **2008**, *69*, 2341. (b) Charmantray, F.; Demeunynck, M.; Carrez, D.; Croisy, A.; Lansiaux, A.; Bailly, C.; Colson, P. *J. Med. Chem.* **2003**, *46*, 967. (c) Charmantray, F.; Demeunynck, M.; Carrez, D.; Croisy, A.; Lansiaux, A.; Bailly, C.; Colson, P. *J. Med. Chem.* **2003**, *46*, 967. (d) Fixler, N.; Demeunynck, M.; Duflos, A.; Lhomme, J. *Heterocycles* **1998**, *48*, 755.

(7) A slightly lower yield was achieved with HCl in wet MeOH.

(8) As the corresponding form of a methylene leaving group, HCHO is smaller than PhCHO or another aldehyde.