

1,3-Dipolar Cycloadditions of 4-Acetoxy Allenates: Access to 2,3-Dihydropyrazoles, 2,3-Dihydroisoxazoles, and Indolizines

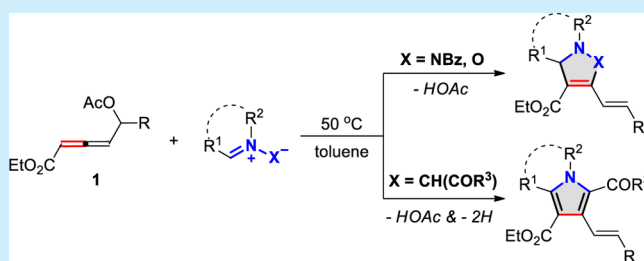
Falin Li,[†] Jiangfei Chen,[‡] Yading Hou,[‡] Yujie Li,[‡] Xin-Yan Wu,[†] and Xiaofeng Tong^{*,†,‡}

[†]Shanghai Key Laboratory of Functional Materials Chemistry, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

[‡]Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, 1 Gehu Road, Changzhou 213164, China

Supporting Information

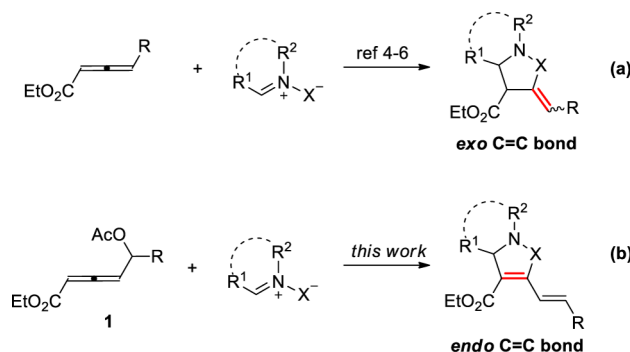
ABSTRACT: The thermal 1,3-dipolar cycloadditions of 4-acetoxyallenoates **1** with various dipoles have been reported. When azomethine imines and nitrones are used as the 1,3-dipole partner, the corresponding reactions afford 2,3-dihydropyrazole and 2,3-dihydroisoxazole derivatives, respectively. These reactions might proceed via a thermal 1,3-dipolar cycloaddition and the subsequent elimination of HOAc. In addition, allenoates **1** react well with in situ generated azomethine ylides in which a similar cycloaddition pathway is followed by oxidative aromatization to give indolizine derivatives.



Because of their biological significance and wide synthetic utility, the development of efficient and simple methods for the synthesis of *N*-heterocycles has attracted considerable attention. Among a variety of reported methods, the time-proven 1,3-dipolar cycloadditions represent one of the most powerful and straightforward tools.¹ In this context, the cycloadditions that employed electron-rich allenes as the dipolarophile partner have been extensively investigated, wherein allenes exhibit divergent reactivity due to their two similar cumulative C=C bonds.² Interestingly, electron-poor ones, 2,3-allenoates, have been recognized as a nice 1,3-dipole synthon with the aid of Lewis base catalysts, which are highly reactive toward the 1,3-dipolar-type cycloadditions with electron-poor alkenes and imines.³ Additionally, the capability of allenoates as the dipolarophile partner for the 1,3-dipolar cycloadditions is self-evident^{4–6} and features exclusive participation of the internal C=C bond of allenoate in the event of 1,3-dipolar cycloaddition, thus affording products bearing an *exo*-cyclic C=C bond unit (Scheme 1a). Only a few thermal 1,3-dipolar cycloadditions of allenoates gave the products with an *endo*-cyclic C=C bond.⁷ As a complement, we herein report the cycloadditions of 4-acetoxyallenoates **1** with various 1,3-dipoles, including azomethine imines and nitrones as well as azomethine ylides (Scheme 1b). Importantly, the installation of an acetate group at the C4-position of allenoate **1** appears to facilitate these cycloadditions via the subsequent elimination of one molecule of HOAc, rendering mild reaction conditions and a different array of target structures (Scheme 1b).

As a part of our continuous efforts on the Lewis base catalyzed transformations of acetoxy-modified allenoates⁸ and inspired by the recent reports of phosphine-catalyzed annulations of

Scheme 1. Allenoates as the Dipolarophile in Thermal 1,3-Dipolar Cycloadditions

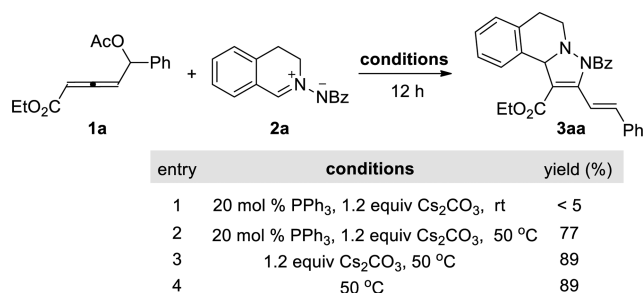


allenoates with 1,3-dipoles,⁹ we attempted to conduct the reaction of allenoate **1a** and azomethine imine **2a** in the presence of PPh₃ (20 mol %) and Cs₂CO₃ (1.2 equiv) in toluene at room temperature (Scheme 2, entry 1). Disappointingly, no reaction was observed. To our delight, a cycloaddition between **1a** and **2a** was triggered through simple elevation of the reaction temperature (50 °C), delivering 2,3-dihydropyrazole **3aa** in 77% isolated yield (Scheme 2, entry 2). The structural assignment was initially supported by NMR and HRMS and later corroborated by X-ray crystallography¹⁰ of product **3fa** (vide infra). However, we were surprised to find that, without PPh₃ catalyst, the reaction was more successful and product **3aa** was obtained in 89% yield (Scheme 2, entry 3). Base additive Cs₂CO₃

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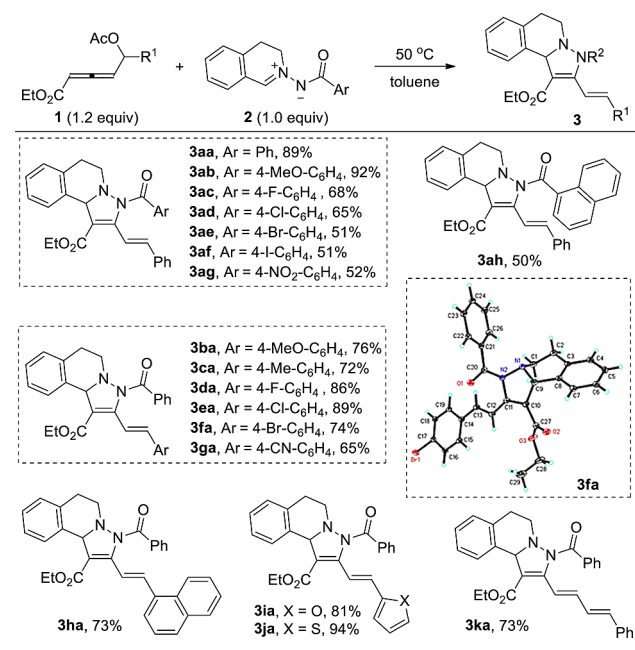
Scheme 2. Preliminary Results of the Reaction of 1a and 2a



was also found not to be necessary at all, although HOAc was generated during the course of the reaction (Scheme 2, entry 4).

These promising results and the bioactive relevance of pyrazoloisoquinoline derivatives¹¹ led us to investigate the generality of this 1,3-dipolar cycloaddition. As shown in Scheme 3,

Scheme 3. 1,3-Dipolar Cycloadditions of Allenates 1 and Azomethine Imines 2



the 1,3-dipolar cycloadditions of allenates 1 and azomethine imines 2 were efficiently achieved with a considerably wide range of substrates. In terms of the imine partner, various benzoyl groups (3aa–ah), including 4-methoxybenzoyl, 4-halobenzoyl, and 4-cyanobenzoyl as well as 1-naphthoyl, could be well tolerated under the thermal cycloaddition conditions. The electron-donating substituents promoted the corresponding reactions more efficiently than those of the electron-withdrawing ones, which might arise from the difference of the nucleophilicity of nitrogen anion. On the other hand, the R¹ group of allenates 1 also exhibited good tolerance. In addition to various phenyl substituents (3ba–ha), heteroaryl (3ia and 3ja) and styryl (3ka) could be readily incorporated. It should be noted that no reactions were observed between 2a and allenates 1 with an alkyl R¹ substituent (not shown), demonstrating the limitation of this thermal 1,3-dipolar cycloaddition.

As a much more readily available 1,3-dipole, azomethine imines 4 are widely employed in the 1,3-dipolar cycloadditions. We were pleased to find that azomethine imines 4 also exhibited

good activity toward 1,3-dipolar cycloaddition with allenates 1, and the results are summarized in Table 1. A wide range of aryl

Table 1. Cycloadditions of 1 with Azomethine Imines 4a

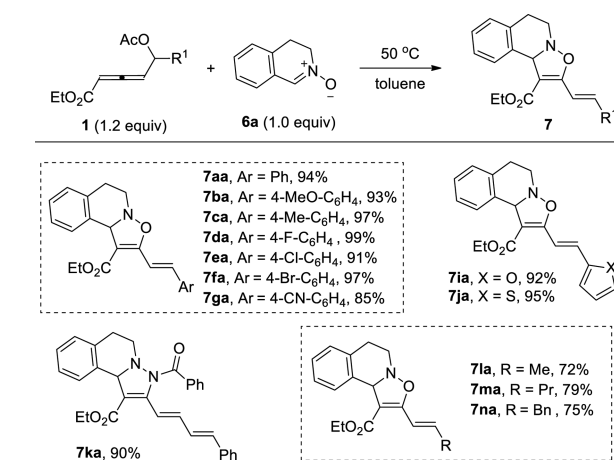
entry	1 (R ¹)	4 (Ar)	5	yield ^b (%)
1	1a (Ph)	4a (Ph)	5aa	72
2	1a	4b (4-FC ₆ H ₄)	5ab	64
3	1a	4c (4-ClC ₆ H ₄)	5ac	53
4	1a	4d (4-MeC ₆ H ₄)	5ad	53
5	1a	4e (4-MeOC ₆ H ₄)	5ae	64
6	1l (Me)	4f (4-NO ₂ C ₆ H ₄)	5lf	50
7	1m (Pr)	4f	5mf	51
8	1n (Bn)	4f	5nf	50

^aReaction conditions: 1 (0.24 mmol), 4 (0.2 mmol), toluene (2 mL), 50 °C. ^bIsolated yield.

groups with electron-donating or -withdrawing substituents of 4 could be tolerated, delivering the corresponding products 5aa–ae in moderate yields (Table 1, entries 1–5). In sharp contrast to imines 2, imine 4 smoothly underwent cycloadditions with the allenates 1 bearing an alkyl R¹ substituent at the C4 position. Indeed, the reactions of imine 4f with allenates 1l–n afforded the corresponding products 5lf–nf in ca. 50% yields (Table 1, entries 6–8).

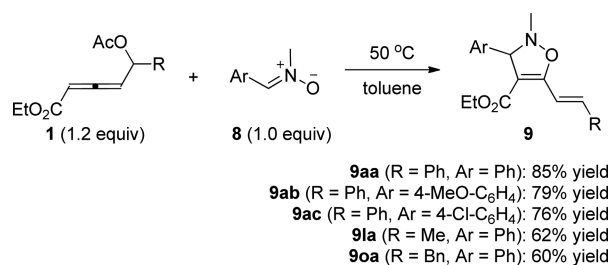
To further demonstrate the potential of allenates 1 toward thermal cycloaddition, the reaction of 1a with nitron 6a was conducted under the same conditions. We were delighted to find that the corresponding cycloaddition product 7aa was isolated in 94% yield. As shown in Scheme 4, the cycloadditions of allenates

Scheme 4. 1,3-Dipolar Cycloadditions of Allenates 1 and Nitron 6a



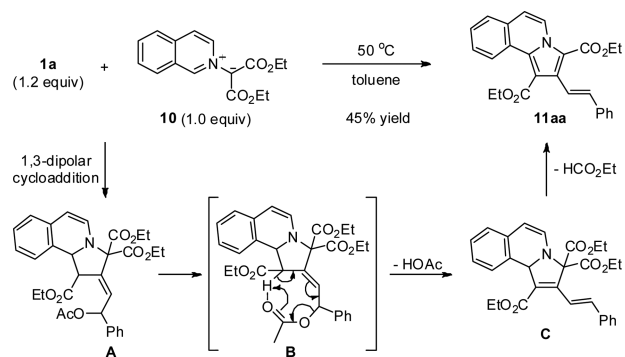
1 and nitron 6a exhibited high efficiency. Essentially quantitative isolated yields were obtained in the cases of allenates 1b–k with an aryl substituent. Allenates 1l–n with an alkyl R¹ substituent were also applicable, but in relatively lower efficiency, affording the corresponding products 7la–na in 72–79% yields.

Compared to cyclic nitron 6a, acyclic nitrones 8a–c were somewhat less reactive for the 1,3-dipolar cycloadditions with allenates 1 (Scheme 5). The reaction of nitron 8a with

Scheme 5. 1,3-Dipolar Cycloadditions of Allenates **1** and Nitrones **8**

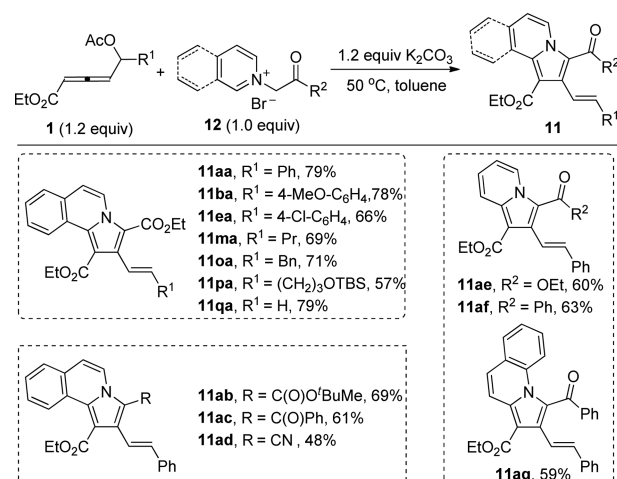
allenoate **1a** afforded the cycloaddition product **9aa** in 85% yield. For the cases of nitrones **8b** and **8c**, the yields of products **9ab** and **9ac** significantly dropped to 79% and 76%, respectively. Furthermore, acyclic nitrone **8a** also reacted with allenates **1** with an alkyl R¹ substituent (**1l** and **1o**), delivering the corresponding products in moderate yields.

To emphasize the general applicability of allenates **1** for the 1,3-dipolar cycloaddition, we finally extended the dipole partner to azomethine ylide **10**. Again, allenoate **1a** and azomethine ylide **10** readily underwent dipolar cycloaddition to give pyrrolo[2,1-*a*]isoquinoline derivative **11aa** in 45% yield. In this process, one molecule each of HOAc and HCO₂Et were eliminated. Although the detailed mechanism was not clear at this stage, a plausible explanation for the formation of product **11aa** was presented in Scheme 6. Following the general

Scheme 6. 1,3-Dipolar Cycloaddition of Allenoate **1a** and Azomethine Ylide **10**

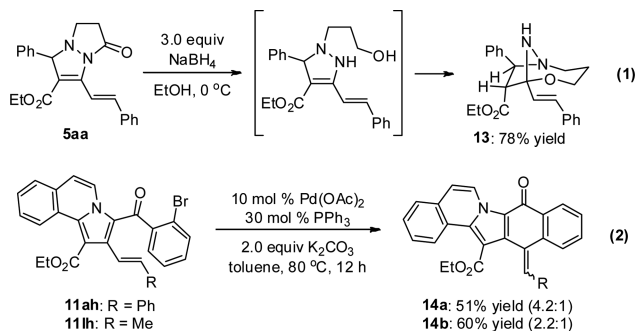
cycloaddition of allenoate and 1,3-dipole,^{4–7} a similar cycloaddition adduct **A** was believed to be formed first. Likely due to its liable deprotonation of ester α -H and ready leaving character of allyl acetoxy, adduct **A** would eliminate one molecule of HOAc via transition state **B**, leading to the generation of intermediate **C**. These two steps might also be involved in the cycloaddition of allenoate **1** with azomethine or nitrone. Finally, intermediate **C** underwent the elimination of HCO₂Et to yield product **11aa**. The process of HCO₂Et elimination was similar to that of the 1,3-dipolar cycloaddition of azomethine ylide and alkyne.¹²

To our delight, the azomethine ylide involved cycloaddition with allenoate **1a** could be realized more efficiently using in situ generated azomethine ylide from the reaction of isoquinolinium derivative **12a** and K₂CO₃, delivering the same product **11aa** in 79% yield (Scheme 7). It was noteworthy to point out that this alternative cycloaddition exhibited wide substrate scope in terms of both allenoate **1** and azomethine ylide partners. Furthermore, this protocol could be successfully extended to pyridinium and

Scheme 7. 1,3-Dipolar Cycloadditions of Allenates **1** and Pyridinium Derivatives **11** with the Aid of K₂CO₃

isoquinolinium derivatives, affording the corresponding products **11ae–af** in ca. 60% yields. For all of these cases, the formation of indolizines **11** would involve an additional aromatization step via air oxidation.

The synthetic utility of the cycloaddition products can be demonstrated by simple chemical manipulations. For instance, upon treatment of NaBH₄, cycloaddition product **5aa** was readily converted into a novel NH-bridged bicycle **13** as a single isomer in 78% yield (eq 1). The formation of **13** might proceed via the reduction of pyrazolidinone and the subsequent intramolecular oxa-Michael addition. Moreover, using a common Heck reaction condition, novel large π -conjugated systems **14a** and **14b** were obtained from cycloaddition products **11ah** and **11lh**, respectively (eq 2).



In summary, we have established that 4-acetoxyallenates **1** as a versatile dipolarophile are capable of undergoing 1,3-dipolar cycloaddition with various dipoles, including azomethine imine, nitrone, and azomethine ylide, affording the cycloaddition products with an endocyclic C=C bond. The wide array of target structures arose from the elimination of HOAc. Efforts are under way to realize the asymmetric variant using chiral metal complex catalysts and 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.5b02724.

Experimental procedures; spectral data for all novel compounds; NMR spectra of obtained compounds (PDF)
X-ray data of **3fa** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tongxf@ecust.edu.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For selected reviews, see: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003. (b) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105. (c) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (d) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (e) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366.
- (2) For reviews, see: (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (b) Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2009**, *13*, 1406.
- (3) For selected reviews, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (d) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (e) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (f) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (g) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588. (h) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. *Beilstein J. Org. Chem.* **2014**, *10*, 2089. (i) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (j) Wang, S.-X.; Han, X. Y.; Zhong, F. R.; Wang, Y. Q.; Lu, Y. *Synlett* **2011**, *2011*, 2766. (k) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 1724. (l) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927.
- (4) For selected examples of cycloadditions of allenates with nitrones, see: (a) Kawai, T.; Kodama, K.-h.; Ooi, T.; Kusumi, T. *Tetrahedron Lett.* **2004**, *45*, 4097. (b) Padwa, A.; Matzinger, M.; Tomioka, Y.; Venkatramanan, M. K. *J. Org. Chem.* **1988**, *53*, 955. (c) Wilkens, J.; Kuhling, A.; Blechert, S. *Tetrahedron* **1987**, *43*, 3237. (d) Zhao, B.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2973. (e) Wu, X.; Na, R.; Liu, H.; Liu, J.; Wang, M.; Zhong, J.; Guo, H. *Tetrahedron Lett.* **2012**, *53*, 342.
- (5) For selected examples of cycloadditions of allenates with azomethine ylides, see: (a) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946. (b) Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 4050. (c) Xue, Z.-Y.; Fang, X.; Wang, C.-J. *Org. Biomol. Chem.* **2011**, *9*, 3622. (d) Laia, F. M. R.; Pinho e Melo, T. M. V. D. *Tetrahedron Lett.* **2009**, *50*, 6180. (e) Zheng, H.-F.; Yu, Z.-H.; Yuan, W.; Tang, Z.-L.; Clough, J.; Gu, Y.-C.; Shi, D.-Q. *Chem. - Eur. J.* **2014**, *20*, 1711.
- (6) For selected examples of cycloadditions of allenates with azomethine imines, see: (a) Zhang, L.; Jing, C.; Liu, H.; Wang, B.; Li, Z.; Jiang, H.; Yu, H.; Guo, H. *Synthesis* **2012**, *45*, 53. (b) Li, Z.; Yu, H.; Zhang, L.; Liu, H.; Na, R.; Bian, Q.; Wang, M.; Guo, H. *Org. Chem.* **2014**, *11*, 220. (c) Wu, C.; Wang, Q.; Zhao, J.; Li, P.; Shi, F. *Synthesis* **2012**, *44*, 3033.
- (7) (a) Na, R.; Liu, H.; Li, Z.; Wang, B.; Liu, J.; Wang, M.-A.; Wang, M.; Zhong, J.; Guo, H. *Tetrahedron* **2012**, *68*, 2349. (b) Wang, C.-S.; Zhu, R.-Y.; Zheng, J.; Shi, F.; Tu, S.-J. *J. Org. Chem.* **2015**, *80*, 512.
- (8) (a) Gu, Y.; Hu, P.; Ni, C.; Tong, X. *J. Am. Chem. Soc.* **2015**, *137*, 6400. (b) Gu, Y.; Li, F.; Hu, P.; Liao, D.; Tong, X. *Org. Lett.* **2015**, *17*, 1106. (c) Hu, P.; Hu, J.; Jiao, J.; Tong, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 5319. (d) Hu, J.; Dong, W.; Wu, X.-Y.; Tong, X. *Org. Lett.* **2012**, *14*, 5530. (e) Li, K.; Hu, J.; Liu, H.; Tong, X. *Chem. Commun.* **2012**, *48*, 2900. (f) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550.
- (9) (a) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (b) Liu, J.; Liu, H.; Na, R.; Wang, G.; Li, Z.; Yu, H.; Wang, M.; Zhong, J.; Guo, H. *Chem. Lett.* **2012**, *41*, 218. (c) Jing, C.; Na, R.; Wang, B.; Liu, H.; Zhang, L.; Liu, J.; Wang, M.; Zhong, J.; Kwon, O.; Guo, H. *Adv. Synth. Catal.* **2012**, *354*, 1023. (d) Wang, D.; Lei, Y.; Wei, Y.; Shi, M. *Chem. - Eur. J.* **2014**, *20*, 15325. (e) Li, Z.; Yu, H.; Feng, Y.; Hou, Z.; Zhang, L.; Yang, W.; Wu, Y.; Xiao, Y.; Guo, H. *RSC Adv.* **2015**, *5*, 34481. (f) Jia, Z.-J.; Daniliuc, C. G.; Antonchick, A. P.; Waldmann, H. *Chem. Commun.* **2015**, *51*, 1054.
- (10) The crystallographic coordinates of **3fa** have been deposited as CCDC 1425328. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre at deposit@ccdc.cam.ac.uk.
- (11) (a) Cruz, R.; Arias, M. E.; Soliveri, J. *Appl. Microbiol. Biotechnol.* **2000**, *53*, 480. (b) Cruz, R.; Arias, M. S.; Arias, M. E.; Soliveri, J. *J. Antibiot.* **1996**, *49*, 700. (c) Paronikyan, E. G.; Sirakanyan, S. N.; Noravanyan, A. S.; Paronikyan, R. G.; Dzhagatspanyan, I. A. *Pharm. Chem. J.* **2001**, *35*, 8. (d) Watanabe, K.; Kamuro, Y.; Taniguchi, E. *J. Agric. Food Chem.* **1994**, *42*, 2311. (e) Watanabe, K.; Taniguchi, E. *Agric. Biol. Chem.* **1986**, *50*, 2591. (f) Toja, E.; Omodei-Sale, A.; Cattaneo, C.; Galliani, G. *Eur. J. Med. Chem.* **1982**, *17*, 223.
- (12) (a) Matsumoto, K.; Ikemi, Y.; Konishi, H.; Shi, X.-L.; Uchida, T. *Heterocycles* **1988**, *27*, 2557. (b) Matsumoto, K.; Hayashi, N.; Ikemi, Y.; Toda, M.; Uchida, T.; Aoyama, K.; Miyakoshi, Y. *J. Heterocycl. Chem.* **2001**, *38*, 371. (c) Matsumoto, K.; Hayashi, N.; Kawajiri, N.; Uchida, T. *Heterocycles* **2005**, *66*, 175.