Heterocycles

International Edition: DOI: 10.1002/anie.201511730
German Edition: DOI: 10.1002/ange.201511730

Water-Assisted Nitrile Oxide Cycloadditions: Synthesis of Isoxazoles and Stereoselective Syntheses of Isoxazolines and 1,2,4-Oxadiazoles

*Chatchai Kesornpun, Thammarat Aree, Chulabhorn Mahidol, Somsak Ruchirawat, and Prasat Kittakoop**

Abstract: *Conventional methods generate nitrile oxides from oxime halides in organic solvents under basic conditions. However, the present work revealed that water-assisted generation of nitrile oxides proceeds under mild acidic conditions (pH 4–5). Cycloadditions of nitrile oxides with alkynes and alkenes easily occurred in water without using catalysts, thus yielding isoxazoles and isoxazolines, respectively, with excellent stereoselectivity toward five- and six-membered cyclic alkenes. A double stereoselective cycloaddition of two units of a nitrile oxide with cyclohexene was also achieved, thus yielding 1,2,4-oxadiazole derivatives having a unique hybrid isoxazoline-oxadiazole skeleton. Enantiomerically pure isoxazolines were prepared from monoterpenes with a ring strain. In one case, the isoxazoline with a butterfly-like structure was simply prepared, and it might be used as a ligand in asymmetric catalysis.*

The chemistry of nitrile oxides is well established, particularly for the synthesis of isoxazoles, isoxazolines, and oxadiazoles.[1] Isoxazoline scaffolds are found in many biologically active compounds,[2] while isoxazoles exhibit various biological activities,[3] and its scaffold is found in many drugs, for example, flucloxacillin, valdecoxib, and dicloxacillin. 1,2,4-Oxadiazoles are important scaffolds in advanced materials and bioactive compounds.[4] Normally, isoxazolines and isoxazoles are synthesized by a cycloaddition of nitrile oxides with alkenes and alkynes. It has long been known that the generation of nitrile oxides from oxime halides occurs under basic conditions (Figure 1). Therefore, the synthesis of isoxazolines and isoxazoles is carried out in solvents containing bases as catalysts.[1,5] However, isoxazolines and isoxazoles can also be prepared by other methods, for example, using transition-metal catalysts (ruthenium or palladium),[6] silver-mediated radical cyclization of ketoximes and 1,3-dicarbonyl compounds,[7] copper nitrate trihydrate as a source of nitrile oxides,[8] copper-catalyzed oxyazidation of unactivated alkenes,[9] and an asymmetric hydroxylamine/enone cascade reaction.[10] Cycloaddition of a nitrile oxide and alkyne is also widely used in click chemistry, particularly for nucleic acids and materials chemistry,[11] and such a cycloaddition is strictly performed either under basic conditions or using metal catalysts. Organic reactions in water can not only be considered green chemistry (abundance in nature and environmentally friendly solvent), but also have the advantage of being run in biological systems (e.g., click reactions, bioconjugation, and bioorthogonal chemistry). As part of our research program directed at green chemistry approaches for the synthesis of bioactive molecules,[12] we report herein the synthesis of isoxazolines, 1,2,4-oxadiazoles, and isoxazoles in aqueous solutions. Since the reactions in water have both environmental and economic advantages, efforts to generate the nitrile oxide in water have been made for the synthesis of isoxazolines and isoxazoles.[13] Herein we show that nitrile oxides can be generated from oxime halides in catalyst-free aqueous solutions, and that the cycloaddition of nitrile oxide with alkenes and alkynes occurs under acidic conditions, rather than under the conventional basic conditions (Figure 1).

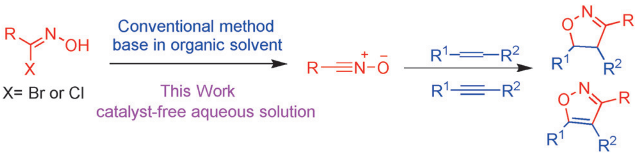


Figure 1. Synthesis of isoxazolines and isoxazoles.

We first examined the catalyst-free synthesis of isoxazoline using the coupling of **1a** and **2a** (Figure 2) as a model reaction, thus giving the isoxazoline **3aa** and the dimer **1aa** as products.[14] We found that alkenes with an amine group gave trace amounts of isoxazoline,[14] thus suggesting that the pH of the reaction mixture has significant influence on the yield. Further experiments revealed that the generation of nitrile oxide is assisted by water, and that the cycloaddition reaction is pH dependent.[14] The presence of water was found to be essential for the reaction.[14] Investigation of the pH effects on the formation of **3aa** in a phosphate buffer revealed that the optimum reaction conditions were at pH 4–5.[14] Note that yields (51–60%) for the reactions at neutral conditions (pH 6–7) were relatively high, thus suggesting that this method is applicable to research dealing with biomolecules, for example, bioconjugation and bioorthogonal chemistry.

---

[*] C. Kesornpun, Prof. Dr. C. Mahidol, Prof. Dr. S. Ruchirawat, Dr. P. Kittakoop
Chulabhorn Graduate Institute, Chemical Biology Program
Kamphaeng Phet 6 Road, Laksi, Bangkok 10210 (Thailand)
E-mail: prasat@cri.or.th
Dr. T. Aree
Department of Chemistry, Faculty of Science
Chulalongkorn University, Bangkok 10330 (Thailand)
Prof. Dr. C. Mahidol, Prof. Dr. S. Ruchirawat, Dr. P. Kittakoop
Chulabhorn Research Institute, Bangkok 10210 (Thailand)
Prof. Dr. S. Ruchirawat, Dr. P. Kittakoop
Center of Excellence on Environmental Health and Toxicology (EHT), CHE, Ministry of Education (Thailand)

Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201511730.

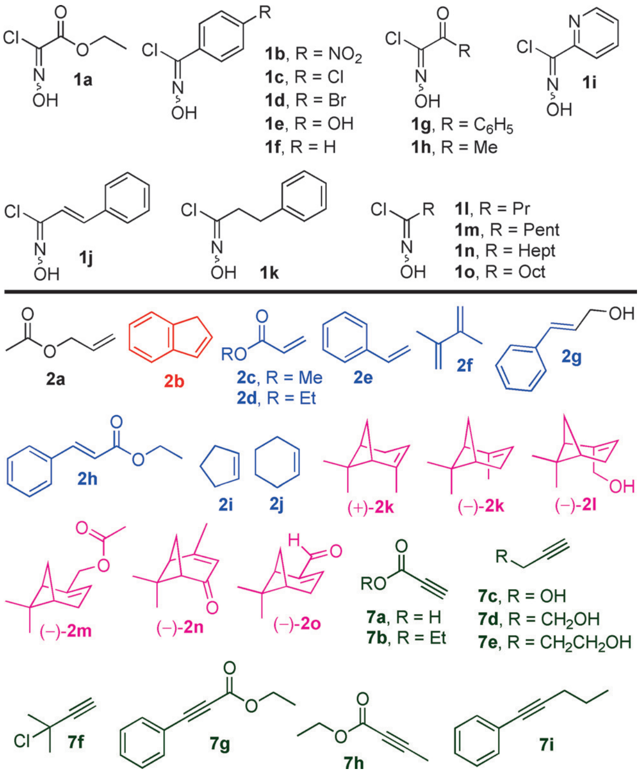
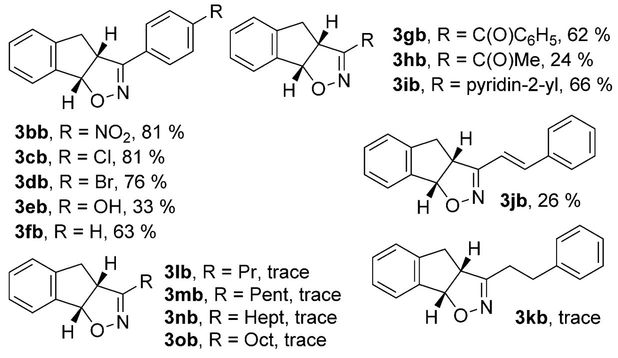


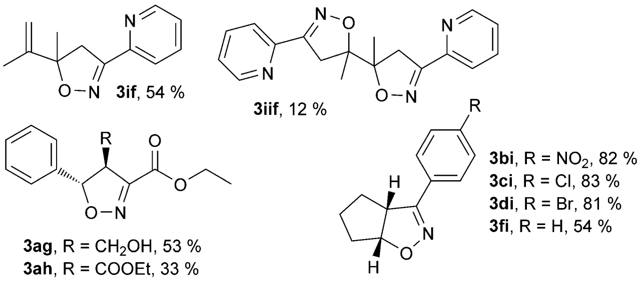
Figure 2. Oxime chlorides (**1a**–**o**) and dipolarophiles (**2a**–**o** and **7a**–**i**) used in this study. Dipolarophiles: (**2b**; red) gave products in Scheme 1; (**2c**–**j**; blue) gave products in Schemes 2 and 3; (**2k**–**o**; pink) gave products in Scheme 4; (**7a**–**i**; green) gave products in Scheme 5.

Next, the scope for oxime chloride substrates was investigated by exploring the reactions of indene (**2b**) with different oxime chlorides (**1b**–**o**) (Figure 2) in a phosphate buffer at pH 4.0 (Scheme 1). Note that acetone was added to the reaction because it increased the substrate solubility. Effects of electron-withdrawing groups (EWG) and electron-donating groups (EDG) were studied using aromatic oxime chlorides substituted with either EWGs (NO_2, Cl, and Br (**1b**–**d**)) or an EDG (**1e**), or without any substitution (**1f**). The oxime chlorides **1b**–**d** gave high product yields (76–81%; **3bb**–**db**), while those with **1e** and **1f** led to lower yields of 33% (**3eb**) and 63% (**3fb**), respectively. These results implied that the EWGs enhanced the isoxazoline formation. Both the oxime chlorides **1g** and **1h** have a C2 ketone, but the yield of **3gb** (62%) was more than that of **3hb** (24%) because **1g** has an EWG (aromatic ring). The oxime chloride **1i** also has an EWG (pyridin-2-yl), thus giving a relatively high yield (66%) of **3ib**. The oxime chloride **1j** gave the isoxazoline **3jb** with 26% yield, but its corresponding saturated derivative **1k** did not give **3kb**, thus supporting the fact that an EWG at C2 of the oxime chlorides is critically important for the reaction. As expected, oxime derivatives (**1l**–**o**), lacking an EWG at C2 did not give the products **3lb**–**ob**. Note that only isoxazolines having a *cis* configuration were obtained from **2b**, as revealed by X-ray analysis of **3bb** and **3ib**.[15]



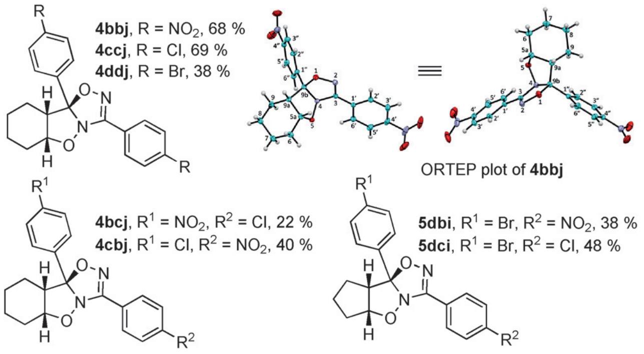
Scheme 1. Synthesis of isoxazolines. Reaction conditions: oxime chloride (1.2 equiv), **2b** (1.0 equiv), acetone (0.5 mL), 0.1 M phosphate buffer (10.0 mL), pH 4.0, RT, 15 h.

Next we investigated the reactivity of oxime chlorides toward terminal and internal alkenes. Terminal alkenes (**2c**–**f**; Figure 2) reacted with oxime chlorides (**1a** or **1b** or **1i**), thus giving the isoxazolines **3ac**, **3bc**, **3id**, and **3ie**. with respective yields of 71, 51, 60, and 92% (see Figure 2S in the Supporting Information).[16] The diene **2f** reacted with **1i**, thus giving isoxazoline **3if** (54%) and bisoxazoline **3iif** (12%; Scheme 2). These isoxazolines have quaternary carbon center. The internal alkenes **2g** and **2h** reacted with **1a**, thus yielding **3ag** (53%) and **3ah** (33%), respectively. Normally, isoxazolines with a $J_{\text{H-4,H-5}}$ value of about 8 Hz are *trans* isomers, while those with a J value of about 12 Hz are *cis* forms.[17] The $J_{\text{H-4,H-5}}$ value of about 8 Hz for both **3ag** and **3ah** indicate that they are *trans* isomers, thus suggesting that the reaction with internal alkenes selectively gives *trans* isoxazolines. The isoxazolines **3bi**–**di** and **3fi** were obtained from cyclopentene (**2i**) in good yields, and they were *cis* isomers as revealed by X-ray analysis of **3bi**.[15]



Scheme 2. Synthesis of isoxazolines. Reaction conditions: oxime chloride (1.2 equiv), alkenes (1.0 equiv), acetone (0.5 mL), 0.1 M phosphate buffer (10.0 mL), pH 4.0, RT, 15 h. However, the mole ratio of oxime chloride/alkene for the synthesis of **3bi** and **3di** was 1.0:4.0.

Interestingly, the reaction of cyclohexene (**2j**) and **1b**–**d**, using a mole ratio of 1.2:1.0 for the oxime chloride and alkene, gave the 1,2,4-oxadiazole derivatives **4bbj**, **4ccj**, and **4ddj** (Scheme 3). The products have a unique 6/5/5 ring system, having a hybrid isoxazoline-oxadiazole skeleton derived from a double cycloaddition with two units of the nitrile oxide. However, the less reactive oxime chlorides (i.e., **1a**, **1i**, and **1f**) gave only a single cycloaddition product, that is, **3aj**, **3ij**, and **3fj** with yields of 30%, 14%, and 7%,

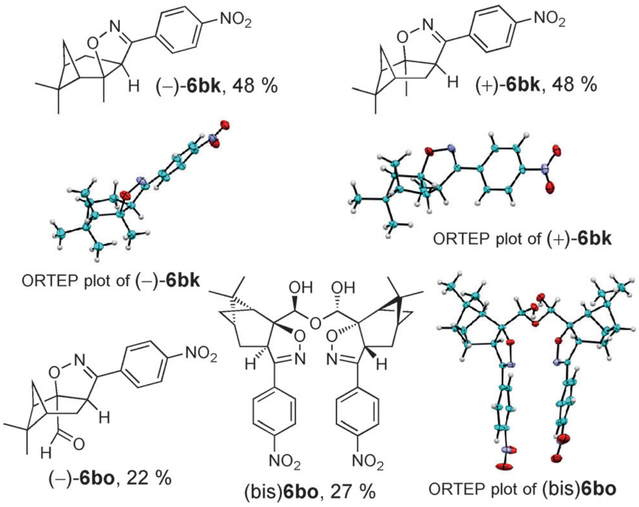


Scheme 3. Synthesis of oxadiazoles. Reaction conditions for formation of **4bbj**, **4ccj**, and **4ddj**: oxime chloride/alkene = 1.2:1.0 equiv, acetone (0.5 mL), 0.1 M phosphate buffer (10.0 mL), pH 4.0, RT, 15 h. Reaction conditions for formation of **4bcj**, **4cbj**, **5dbi**, and **5dci**: oxime chloride/isoxazoline = 2.0:1.0 equiv, acetone (0.2 mL), phosphate buffer (1.0 mL), pH 4.0, RT, 15 h. For ORTEP structures thermal ellipsoids shown at 20% probability.

respectively (see Figure 3S in the Supporting Information).[16] The X-ray analysis[15] of **4bbj** revealed a *cis*-fused 6,5-membered ring, and the isoxazoline unit was perpendicular to the oxadiazole moiety (Scheme 3). Unexpectedly, quaternary carbon center in the 1,2,4-oxadiazole derivatives was stereoselectively constructed under mild reaction conditions. Increasing the mole ratio of the alkene, that is, using a 1:10 ratio for oxime chloride and alkene, gave products of a single cycloaddition (**3bj**, **3cj**, and **3dj** with respective yields of 33 %, 33 %, and 40 %, respectively).[16] Therefore, the alkene mole ratio determines whether oxadiazoles or isoxazolines are formed. We propose that isoxazolines (i.e., **3bj**, **3cj**, and **3dj**) are first formed, and the cycloaddition of a second nitrile oxide to these isoxazolines gives rise to the formation of the corresponding 1,2,4-oxadiazoles. This reaction mechanism prompted us to synthesize 1,2,4-oxadiazoles derived from two different nitrile oxide units. Isoxazolines (i.e., **3bj**, **3cj**, **3dj**, and **3ij**) were prepared with the first nitrile oxide unit, and subsequent cycloaddition with the second nitrile oxide gave the 1,2,4-oxadiazoles **4bcj**, **4cbj**, **4ibj**, and **4idj**, respectively (Scheme 3 and Figure 3S).[16] Moreover, the method was used for isoxazolines derived from **2i**, thus giving oxadiazoles with a unique 5/5/5 ring system, that is, **5dbi**, **5dci**, and **5idi** (Scheme 3 and Figure 3S).[16] Although several oxadiazoles have been synthesized through nitrile oxide chemistry,[1,13e] the preparation of the novel hybrid isoxazoline-oxadiazoles presented here has never been reported. Moreover, the stereoselective synthesis of these oxadiazoles was achieved under mild conditions.

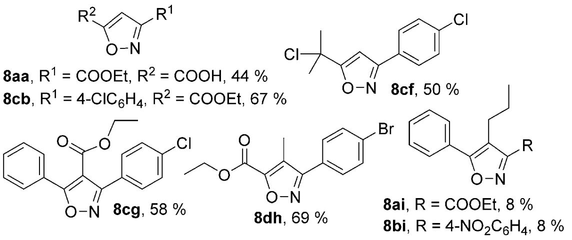
Since the cycloaddition reaction in mild acidic aqueous solution is stereoselective, we next aimed to utilize this method for the synthesis of enantiomerically pure isoxazolines. In addition to being important scaffolds in bioactive molecules, isoxazolines are used as ligands in asymmetric catalysis.[18] It is known that the cycloaddition of nitrile oxides with norbornene and derivatives proceed with *exo*-stereoselectivity, however, two possible isomers (*anti* and *syn*) were obtained from the reaction.[19] Monoterpenes, such as α-pinene (**2k**) and (1*R*)-(−)-myrtenol [(−)-**2l**], have similar ring strain to that of norbornene, therefore we selected these monoterpenes for the cycloaddition. These terpenes have an sp^2-hybridized quaternary carbon center, and we anticipated that the newly generated quaternary carbon center in the isoxazoline products would have the same stereoselectivity as that in oxadiazoles (Scheme 3).

The enantiomerically pure monoterpene, (1*R*)-(+)-α-pinene [(+)-**2k**], reacted with **1b** to yield 48 % of the isoxazoline having a negative optical rotation, that is (−)-**6bk** (Scheme 4). The reaction gave (−)-**6bk** as a single product, thus implying that only one enantiomer was obtained from the reaction. In contrast, the enantiomer, (1*S*)-(−)-α-pinene [(−)-**2k**], yielded the isoxazoline with a positive optical rotation, (+)-**6bk**, in a yield of 48 %. X-ray analysis[15] confirmed the structures of (−)-**6bk** and (+)-**6bk**. The reaction of (+)-**2k** with **1a** and **1i** gave (−)-**6ak** (48 % yield) and (−)-**6ik** (21 % yield), respectively (see Figure 4S in the Supporting Information).[16] Enantiomerically pure terpenes, (1*R*)-(−)-myrtenol [(−)-**2l**], (1*R*)-(−)-myrtenyl acetate [(−)-**2m**], and (1*S*)-(−)-verbenone [(−)-**2n**] reacted with **1b**, thus giving (+)-**6bl** (41 %), (−)-**6bm** (51 %), and (−)-**6bn** (74 %), respectively (see Figure 4S in the Supporting Information).[16] Interestingly, (1*R*)-(−)-myrtenal [(−)-**2o**] gave (−)-**6bo** (22 % yield) and the bis(acetal) derivative (bis)**6bo** (27 % yield; Scheme 4). It was found that (−)-**6bo** was easily converted into (bis)**6bo** during crystallization, and it has a plane of symmetry (*meso* form), and its butterfly-like structure was confirmed by X-ray analysis (Scheme 4).[15] Such a unique structure is possibly useful as a ligand in asymmetric catalysis.



Scheme 4. Preparation of enantiomerically pure isoxazolines. Reaction conditions: oxime chloride (1.2 equiv), alkene (1.0 equiv), acetone (0.5 mL), 0.1 M phosphate buffer (10.0 mL), pH 4.0, RT, 15 h. For ORTEP structures thermal ellipsoids shown at 20% probability.

Next we preliminarily investigated the catalyst-free cycloaddition for the synthesis of isoxazoles. The external alkynes **7a–f** (Figure 2) reacted with either **1a** or **1c**, thus giving the isoxazoles **8aa**, **8cb**, **8ac**, **8cd**, **8ce**, and **8cf** with yields of 44 %, 67 %, 32 %, 77 %, 40 %, and 50 %, respectively (Scheme 5 and



Scheme 5. Synthesis of isoxazoles. Reaction conditions: oxime chloride (1.2 equiv), alkyne (1.0 equiv), acetone (0.5 mL), 0.1 M phosphate buffer (10.0 mL), pH 4.0, RT, 15 h.

see Figure 5S in the Supporting Information).[16] Note that the catalyst-free cycloaddition could be employed with either an acid (**7a**) or alcohols (**7c**–**e**) without functional-group protection. The internal alkynes **7g** and **7h** selectively gave the isoxazoles **8cg** (58%) and **8dh** (69%), respectively. However, the internal alkyne **7i** gave the major isomers **8ai** and **8bi** (each with 8% yield), together with a trace amount of the minor isomer (observed from ^{1}H NMR spectra of crude reaction mixtures).

In conclusion, we have demonstrated for the first time that nitrile oxides can be generated from oxime halides in aqueous solution without using any catalysts. The formation proceeds under mild acidic conditions, as opposed to basic conditions which have long been known as the conventional method. The cycloaddition of nitrile oxides with certain alkenes in aqueous solution had excellent stereoselectivity, and it was used for the synthesis of 1,2,4-oxadiazoles and enantiomerically pure isoxazolines. The catalyst-free cycloaddition was also used for the synthesis of isoxazoles. We propose that the formation of nitrile oxide from oxime chloride in water is initiated by the loss of a chlorine atom from the oxime chloride with subsequent abstraction of the oxime proton by chloride ion. Nitrile oxide is well dissolved in water because it is charged, thus the solubility drives the reaction forward and favors the production of the nitrile oxide in water (see Scheme 5S in the Supporting Information).[20]

Acknowledgements

This work is supported by the Center of Excellence on Environmental Health and Toxicology, Science & Technology Postgraduate Education and Research Development Office (PERDO), Ministry of Education. T. Aree thanks the Ratchadapisek Sompoch Endowment Fund, Chulalongkorn University (CU-58-021-FW) and the National Research University Project of Thailand (WCU-58-013-FW) for financial support.

Keywords: alkenes · cycloaddition · green chemistry · heterocycles · water

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3997–4001
Angew. Chem. **2016**, *128*, 4065–4069

[1] L. I. Belen'kii, in *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed. (Ed.: H. Feuer), Wiley, Hoboken, **2008**, pp. 1–127.

[2] a) K. Kaur, V. Kumar, A. K. Sharma, G. K. Gupta, *Eur. J. Med. Chem.* **2014**, *77*, 121–133; b) Y. Ozoe, M. Asahi, F. Ozoe, K. Nakahira, T. Mita, *Biochem. Biophys. Res. Commun.* **2010**, *391*, 744–749; c) A. Soni, A. Rehman, K. Naik, S. Dastidar, M. S. Alam, A. Ray, T. Chaira, V. Shah, V. P. Palle, I. A. Cliffe, V. J. Sattigeri, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1482–1485; d) S. K. Prajapti, S. Shrivastava, U. Bihade, A. K. Gupta, V. G. M. Naidu, U. C. Banerjee, B. N. Babu, *MedChemComm* **2015**, *6*, 839–845; e) C. Dallanoce, P. Magrone, C. Matera, F. Frigerio, G. Grazioso, M. DeAmici, S. Fucile, V. Piccari, K. Frydenvang, L. Pucci, C. Gotti, F. Clementi, C. DeMicheli, *ChemMedChem* **2011**, *6*, 889–903; f) P. Fagone, K. Muthumani, K. Mangano, G. Magro, P. L. Meroni, J. J. Kim, N. Y. Sardesai, D. B. Weiner, F. Nicoletti, *Immunology* **2014**, *142*, 594–602.

[3] a) J. Sun, C. Lin, X. Qin, X. Dong, Z. Tu, F. Tang, C. Chen, J. Zhang, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3129–3134; b) M. G. Perrone, P. Vitale, A. Panella, C. G. Fortuna, A. Scilimati, *Eur. J. Med. Chem.* **2015**, *94*, 252–264; c) S. A. Laufer, S. Margutti, M. D. Fritz, *ChemMedChem* **2006**, *1*, 197–207; d) K. M. Naidu, A. Suresh, J. Subbalakshmi, D. Sriram, P. Yogeeswari, P. Raghavaiah, K. V. Chandra Sekhar, *Eur. J. Med. Chem.* **2014**, *87*, 71–78.

[4] a) A. Pace, P. Pierro, *Org. Biomol. Chem.* **2009**, *7*, 4337–4348; b) J. Guo, R. Hua, Y. Sui, J. Cao, *Tetrahedron Lett.* **2014**, *55*, 1557–1560; c) C. S. Jiang, Y. Fu, L. Zhang, J. X. Gong, Z. Z. Wang, W. Xiao, H. Y. Zhang, Y. W. Guo, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 216–220; d) A. I. Almansour, R. Suresh Kumar, N. Arumugam, D. Sriram, *Eur. J. Med. Chem.* **2012**, *53*, 416–423; e) D. Ding, M. A. Boudreau, E. Leemans, E. Spink, T. Yamaguchi, S. A. Testero, P. I. O'Daniel, E. Lastochkin, M. Chang, S. Mobashery, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4854–4857.

[5] a) N. Lohse-Fraefel, E. M. Carreira, *Chem. Eur. J.* **2009**, *15*, 12065–12081; b) S. Kankala, R. Vadde, C. S. Vasam, *Org. Biomol. Chem.* **2011**, *9*, 7869–7876; c) S. K. Chittimalla, R. Kuppusamy, K. Thiyagarajan, C. Bandi, *Eur. J. Org. Chem.* **2013**, 2715–2723; d) A. Singh, G. P. Roth, *Tetrahedron Lett.* **2012**, *53*, 4889–4891.

[6] a) S. Grecian, V. V. Fokin, *Angew. Chem. Int. Ed.* **2008**, *47*, 8285–8287; *Angew. Chem.* **2008**, *120*, 8409–8411; b) K. Y. Dong, H. T. Qin, F. Liu, C. Zhu, *Eur. J. Org. Chem.* **2015**, *2015*, 1419–1422; c) J. S. Oakdale, R. K. Sit, V. V. Fokin, *Chem. Eur. J.* **2014**, *20*, 11101–11110; d) Z. She, D. Niu, L. Chen, M. A. Gunawan, X. Shanja, W. H. Hersh, Y. Chen, *J. Org. Chem.* **2012**, *77*, 3627–3633.

[7] Y. Y. Liu, X. H. Yang, J. Yang, R. J. Song, J. H. Li, *Chem. Commun.* **2014**, *50*, 6906–6908.

[8] M. Gao, Y. Li, Y. Gan, B. Xu, *Angew. Chem. Int. Ed.* **2015**, *54*, 8795–8799; *Angew. Chem.* **2015**, *127*, 8919–8923.

[9] L. Zhu, H. Yu, Z. Xu, X. Jiang, L. Lin, R. Wang, *Org. Lett.* **2014**, *16*, 1562–1565.

[10] K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* **2010**, *49*, 5762–5766; *Angew. Chem.* **2010**, *122*, 5898–5902.

[11] F. Heaney, *Eur. J. Org. Chem.* **2012**, 3043–3058.

[12] a) R. Sangsuwan, S. Sangher, T. Aree, C. Mahidol, S. Ruchirawat, P. Kittakoop, *RSC Adv.* **2014**, *4*, 13708–13718; b) D. U. Ganihigama, S. Sureram, S. Sangher, P. Hongmanee, T. Aree, C. Mahidol, S. Ruchirawat, P. Kittakoop, *Eur. J. Med. Chem.* **2015**, *89*, 1–12.

[13] a) L. Han, B. Zhang, M. Zhu, J. Yan, *Tetrahedron Lett.* **2014**, *55*, 2308–2311; b) Y. Hou, S. Lu, G. Liu, *J. Org. Chem.* **2013**, *78*, 8386–8395; c) N. Nishiwaki, K. Kobiro, H. Kiyoto, S. Hirao, J. Sawayama, K. Saigo, Y. Okajima, T. Uehara, A. Maki, M. Ariga,

Org. Biomol. Chem. **2011**, *9*, 2832 – 2839; d) H. Asahara, K. Arikiyo, N. Nishiwaki, *Beilstein J. Org. Chem.* **2015**, *11*, 1241 – 1245; e) N. Nishiwaki, K. Kobiro, S. Hirao, J. Sawayama, K. Saigo, Y. Ise, Y. Okajima, M. Ariga, *Org. Biomol. Chem.* **2011**, *9*, 6750 – 6754.

[14] Details of experiments and results are in the Supporting Information.

[15] Details of the single-crystal X-ray analysis and ORTEP plots are in Table 4S and Figure 1S (see the Supporting Information), respectively. CCDC 1434333 – 1434339 ((Bis)**6bo**, (+)-**6bk**, (−)-**6bk**, **4bbj**, **3bi**, **3ib**, and **3bb**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[16] Structures and yields are in the Supporting Information.

[17] X. Qi, Y. Jiang, C. M. Park, *Chem. Commun.* **2011**, *47*, 7848 – 7850.

[18] a) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119 – 3154; b) S. O'Reilly, M. Aylward, C. Keogh-Hansen, B. Fitzpatrick, H. A. McManus, H. Muller-Bunz, P. J. Guiry, *J. Org. Chem.* **2015**, *80*, 10177 – 10186; c) R. K. Gabr, T. Hatakeyama, K. Takenaka, S. Takizawa, Y. Okada, M. Nakamura, H. Sasai, *Chem. Eur. J.* **2013**, *19*, 9518 – 9525; d) R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Pozzi, *Eur. J. Org. Chem.* **2003**, 1191 – 1197; e) D. Goyard, S. M. Telligmann, C. Goux-Henry, M. M. K. Boysen, E. Framery, D. Gueyrard, S. Vidal, *Tetrahedron Lett.* **2010**, *51*, 374 – 377.

[19] a) W. Fliege, R. Huisgen, *Justus Liebigs Ann. Chem.* **1973**, 2038 – 2047; b) K. Gutsmiedl, C. T. Wirges, V. Ehmke, T. Carell, *Org. Lett.* **2009**, *11*, 2405 – 2408; c) J. Tajabadi, M. Bakavoli, M. Gholizadeh, H. Eshghi, M. Izadyar, *RSC Adv.* **2015**, *5*, 38489 – 38498; d) J. R. Nagireddy, E. Carlson, W. Tam, *Can. J. Chem.* **2014**, *92*, 1053 – 1058.

[20] Details of the reaction mechanism, the roles of water and the EWG at C2 of the oxime chlorides, are in the Supporting Information.

Received: December 18, 2015