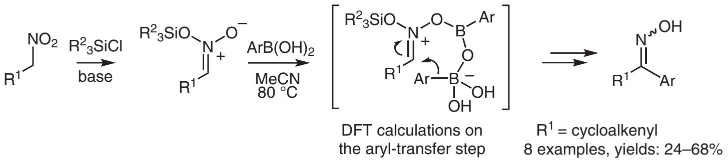
Metal-Free Addition of Boronic Acids to Silylnitronates

Mansour Dolé Kerim[a]
Pakoupati Boyode[b]
Julian Garrec[c]
Laurent El Kaïm*[a]

[a] Laboratoire de Synthèse Organique, CNRS, Ecole Polytechnique, ENSTA Paris - UMR 7652, Institut Polytechnique de Paris, 828 Bd des Maréchaux, 91128 Palaiseau, France
laurent.elkaim@ensta-paristech.fr
[b] Laboratoire de Chimie Organique et des Substances Naturelles, Département de Chimie, Faculté des Sciences, Université de Lomé, BP 1515, Lomé, Togo
[c] Unité Chimie et Procédés, ENSTA Paris – UMR 7652, Institut Polytechnique de Paris, 828 Bd des Maréchaux, 91128 Palaiseau, France



DFT calculations on the aryl-transfer step

R1 = cycloalkenyl
8 examples, yields: 24–68%

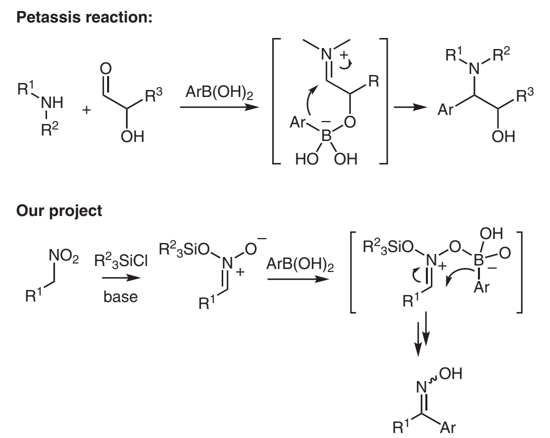
Received: 29.12.2019
Accepted after revision: 10.02.2020

DOI: 10.1055/s-0039-1690845; Art ID: st-2019-d0703-l

Abstract We report for the first time a metal-free addition of boronic acids to silylnitronates to afford oxime derivatives through aryl transfer on the carbon nitrogen double bond. A reaction mechanism has been proposed in relation with a DFT study on the key aryl transfer. This arylation process is effective for cycloalkenyl nitro derivatives leading to oximes that may be oxidatively converted into 3-arylisoxazole derivatives.

Key words nitro, silyl nitronate, boronic acid, oxime, isoxazole

With the development of the Suzuki–Miyaura reaction, boronic acids have been recognized among the most useful arylation reagents.[1] Whereas such reaction requires an activation of the aryl group through a transmetalation process with various transition metals, in the absence of such metal, the boronic acid may still transfer its aryl moiety after prior conversion into a boronate intermediate. Highlighted with the discovery of the Petassis reaction,[2] this seminal Mannich-type behavior of boronic acids has given the impetus for the discovery of many other metal-free arylations and vinylation over the last ten years.[3] However, boronic acids remain moderately nucleophilic species, which often require the installation of an intramolecular aryl transfer through ate-complex formation for efficient couplings.[4] This is the case of the Petassis reaction where the lack of electrophilicity of simple imine derivatives may be overcome by neighboring hydroxy groups (Scheme 1). Following our interest in nitro chemistry and considering known nucleophilic additions on nitronic acid derivatives (Nef-type reactions),[5] we surmised that nitronic acid derivatives might further interact with boronic acids to afford transient ate complexes prone to undergo an intramolecular aryl transfer onto the C–N unsaturated bond (Scheme 1).

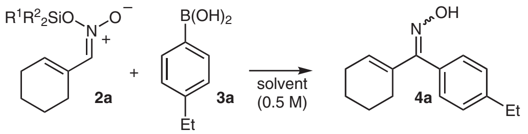

Petassis reaction:

Our project

Scheme 1 Metal-free boronic acid addition to C–N double bonds

Due to the instability of nitronic esters (leading to oximes and aldehydes)[6] or acylnitronates (leading to nitrile oxide at ambient temperature),[7] we decided to focus our study on silylnitronic esters, a relatively stable family of compounds, readily prepared by silylation of nitro derivatives with trialkylsilyl chlorides, whose chemistry has been largely popularized by the studies of Seebach at the beginning of the 1980s.[8]

Due to poor hydrolytic stability of trimethylsilyl nitronates, a bulkier *tert*-butyl-dimethylsilyl group was selected for this study. The *tert*-butyl-dimethylsilylnitronate **2a** was thus prepared in quantitative yield by treatment of nitromethylcyclohexene **1a** with 1.1 equiv of *tert*-butyl-dimethylsilylchloride in the presence triethylamine (1.1 equiv) in dry acetonitrile. Nitronate **2a** could be filtered rapidly through a short silica gel column without significant degradation. When **2a** was heated in acetonitrile together with 4-ethylphenylboronic acid (**3a**) under argon, we were delighted to observe the formation of oxime **4a** resulting from the expected aryl transfer (Scheme 2). The low 17% isolated yield could be slightly increased by selecting toluene as solvent at 80 °C. Finally, the best conditions were obtained using a twofold excess of boronic acid **3a** in acetonitrile at 70 °C (Scheme 2).

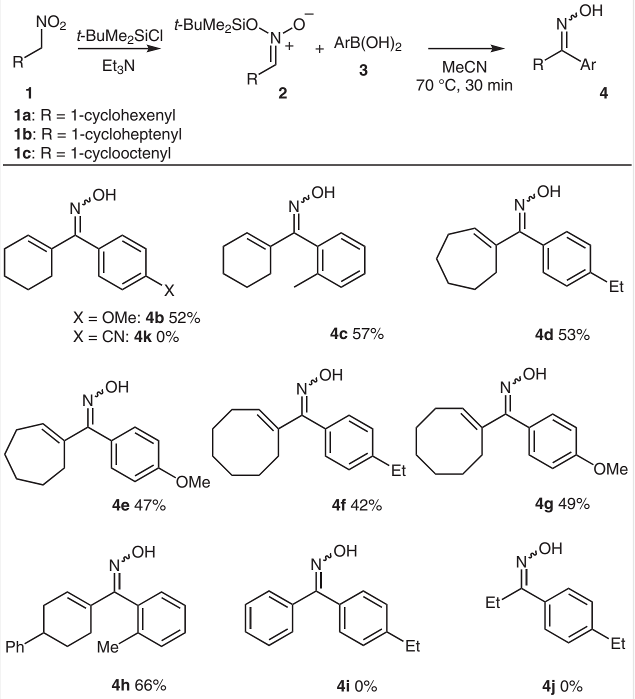


R^1 = *t*-Bu, R^2 = Me, **3a** (1 equiv), acetonitrile (50 °C, 90 min)	17%
R^1 = *t*-Bu, R^2 = Me, **3a** (1 equiv), DMF (50 °C, 90 min)	0%
R^1 = *t*-Bu, R^2 = Me, **3a** (1 equiv), toluene (80 °C, 60 min)	31%
R^1 = *t*-Bu, R^2 = Me, **3a** (2 equiv), toluene (80 °C, 60 min)	61%
R^1 = *t*-Bu, R^2 = Me, **3a** (2 equiv), acetonitrile (50 °C, 60 min)	31%
R^1 = *t*-Bu, R^2 = Me, 3a (2 equiv), acetonitrile (70 °C, 30 min)	68%
R^1 = R^2 = Ph, **3a** (2 equiv), acetonitrile (70 °C, 30 min)	0%

Scheme 2 Optimized conditions for the formation of **4a**

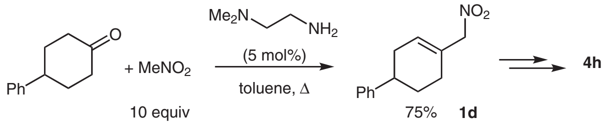
Changing the *tert*-butyldimethyl silyl group by a triphenylsilyl group (Scheme 2) did not result in the formation of **4a** under the same conditions.

To evaluate the scope of this reaction, a set of representative *tert*-butyldimethylsilyl nitronates **2a–c** was prepared in quantitative yields from the corresponding nitro derivatives using the initial procedure, followed by rapid filtration through a short silica plug. The results of their reaction with different arylboronic acids are displayed in Scheme 3.



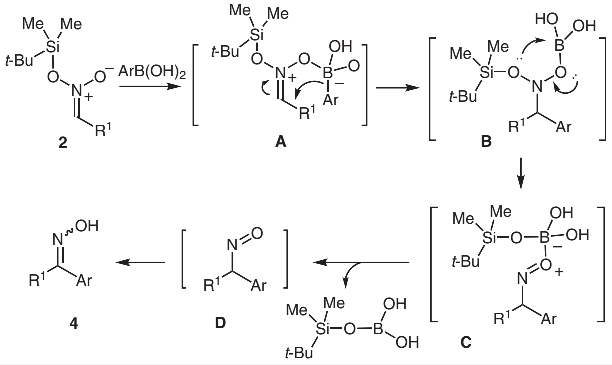
Scheme 3 Scope of the boronic acid addition to silylnitronate

The coupling is only efficient for 1-nitromethylcycloalkenyl derivatives as shown by the various cyclohexenyl, cycloheptenyl, and cyclooctenyl oximes **4** formed in moderate isolated yields from the corresponding silylnitronates. Electron-poor aryl boronic acids did not appear to be effective as shown by the unproductive addition of 4-cyanophenyl boronic acid. Under prolonged heating, only degradation of **2a** was observed, without any formation of **4k**. All oximes were obtained as single diastereomers, however, we failed to determine their *Z*- or *E*-stereochemistry. Surprisingly, the silylnitronate of nitromethylbenzene did not form the expected adduct **4i** with 4-ethylboronic acid. This lack of reactivity was also observed for 1-nitropropane, showing the high sensitivity of this reaction to electronic factors. Though these results limit the scope of this reaction, it should be noted that 1-nitromethylcycloalkenyl derivatives are easily prepared on large scale from their related cycloalkanone derivatives using a Knoevenagel-type condensation with nitromethane.[9] Indeed, this strategy could be readily adapted to access more complex substituted oximes choosing among the relatively wide range of commercially available cycloalkanones. Thus oxime **4h** (Scheme 3) was prepared starting from 4-phenylcyclohexanone, which was efficiently converted into nitro intermediate **1d** on heating in a toluene/nitromethane mixture in the presence of a catalytic amount of *N*,*N* dimethylethylenediamine (Scheme 4).



Scheme 4 4-Phenylcyclohexanone conversion into **1d**

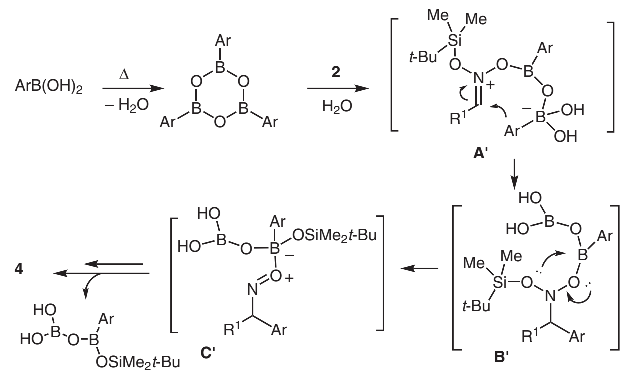
A plausible reaction mechanism for the conversion of the silylnitronates into oximes is presented in Scheme 5. After complexation of the silylnitronate with the boronic acid, aryl transfer affords an unstable intermediate **B**, whose fragmentation leads to chelated nitroso intermediate **C**. Fur-



Scheme 5 Possible mechanism for the conversion of **2** into **4**

ther fragmentation and nitroso–oxime tautomerism give the final compound **4**. An alternative concerted migration/fragmentation of intermediate **B** directly to **D** could also be proposed. The formation of *O*-silyl oximes, which might also have been expected, was not observed.

To gain further insight into the mechanism of this reaction, we performed density functional theory (DFT) calculations to model the aryl transfer from the boric acid to the nitronate moiety. Despite all our efforts to model the aryl transfer from intermediate **A** to intermediate **B** (Scheme 5), we were not able to identify a transition state with an energy barrier lower than 30 kcal mol^{-1}, which is probably associated with a mechanistic pathway unlikely to occur under our reaction conditions. In the Petassis reaction of α-hydroxy aldehydes, the aryl transfer is usually explained via the formation of an intermediate boronate followed by an intramolecular 1,5-shift of the aryl moiety from the boron to the carbon of the imine function.[2] As shown by the results of our models (Figure 1, path A), a similar mechanism as disclosed in Scheme 5 requires that the C,N,O atoms of the nitronate adopt an out-of-plane geometry, which is highly energy demanding. In an attempt to reduce this out-of-plane deformation, we envisaged that a second boron atom might be involved through the intermediacy of boronic anhydrides formed during the reaction (Scheme 6).



Scheme 6 Alternative mechanism for the conversion of **2** into **4** with two boron atoms

Figure 1 summarizes the DFT calculations performed on the crucial aryl transfer steps following the two proposed reaction mechanisms. In pathway A (Scheme 5), the silylnitronate molecule initially forms a noncovalent molecular complex with one single boric acid molecule (state R_A in Figure 1, A). Then the aryl group is transferred from the boric acid moiety to the nitronate moiety in a single step, passing through transition state TS_A and leading to the adduct P_A. As mentioned above, pathway A is associated with a very high free-energy barrier of 34 kcal mol^{-1}. On the other hand, the alternative pathway B (Scheme 6), exhibits a smaller energy barrier of 22 kcal mol^{-1}, corresponding to a reduction in activation free energy of more than 10 kcal mol^{-1} with respect to mechanism A. Most importantly, the transition state of pathway B, namely TS_B, differs substantially from TS_A. Though the formation of a 7-membered ring transition state TS_B might be considered less favorable than the 5-membered ring in TS_A, TS_B is stabilized by an internal H-bond between the terminal boric acid OH group and the oxygen atom that links the silyl to the nitronate moieties. Another key difference between the two transition states lies in the local structure around the nitrogen atom of the nitronate group, as shown in the insets of Figure 1. Indeed, both transition states require a partial disruption of the planarity of the nitronate group, but the geometry distortion is

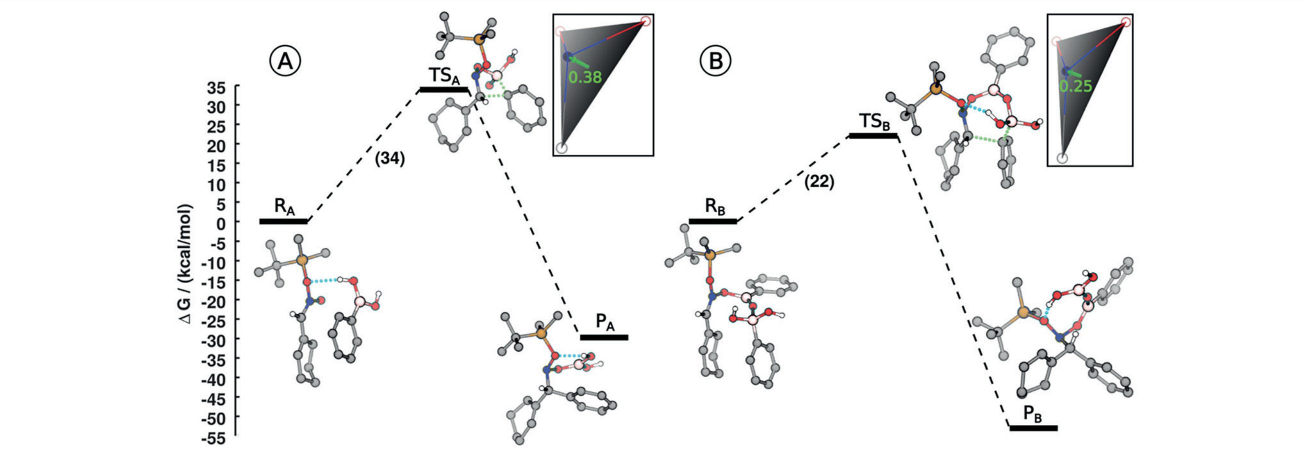
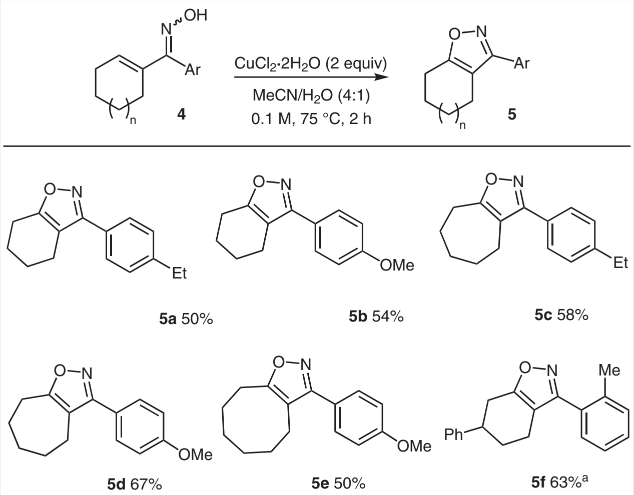


Figure 1 Computed free-energy pathways of the aryl transfer reaction. Insets A and B correspond to pathways A (Scheme 5) and B (Scheme 6), respectively. Optimized molecular structures for each stationary state are represented for each energy level. Most H atoms are hidden for the sake of clarity. Only polar hydrogens and the CH group directly attached to the nitronate moiety are represented. Hydrogen bonds are represented with light-blue dotted lines while forming/breaking bonds at the transition states are represented with green-dotted lines. For each transition state, the out-of-plane deformation of the nitronate group is shown in an inset: The O–C–O plane is shown in black, and the distance in Å between this plane and the nitrogen atom is shown in green.

stronger in TS_A than in TS_B. The computed out-of-plane distance between the nitrogen atom and the O–C–O plane of the nitronate moiety are 0.38 Å and 0.25 Å for TS_A and TS_B, respectively. It should be stressed that even a small difference in planarity may affect the transition states energy substantially, because the out-of-plane distortion tends to disrupt the local delocalization of π electrons, which plays a key role in the stability of the group.

In order to support this mechanistic proposition, we decided to examine the behavior of silyl nitronate **2a** towards phenyl boroxine instead of phenyl boronic acid. Using the former anhydride directly, the key synthetic intermediate displaying two boron atoms complexed to the silyl nitronate should be formed more easily, leading to a potential increase in yield. While heating **2a** with 2.5 equivalents of phenyl boronic acid led to phenyl-cyclohexenyl oxime **4l** in a poor 24% yield after 30 min, heating the same reaction with 1 equivalent of triphenylboroxine led to **4l** in 32% yield. Though not large, this increase in yield supports a potential effect of boronic anhydrides on the mechanism of this reaction.

With these unsaturated oximes in hand, we next examined their conversion into oxazole derivatives. Several conditions for oxidative transformation of α,β-unsaturated oximes into oxazoles have been reported in the literature.[10] The reaction may be observed using various oxidants such as manganese dioxide and copper salts used in stoichiometric quantities or in conjunction with oxygen. Indeed, when oxime **4a** was heated in acetonitrile in the presence of copper chloride we observed the formation of isoxazole **5a** in a moderate 50% isolated yield (Scheme 7). Attempts to perform this reaction in other solvents such as DMF or THF resulted in lower yields. Further optimization for this known transformation was not pursued, and Scheme 7 displays the results of the cyclizations under these conditions. All oximes gave fused isoxazoles **5** in good to moderate yields.



Scheme 7 Formation of isoxazoles **5** from oximes **4**. [a] The reaction was left for 12 h for completion.In conclusion, we have disclosed a new interaction of boronic acids with silyl nitronates.[11] This aryl transfer from a boron atom onto the electrophilic C=N double bond of a nitronate extends the previously disclosed oxime synthesis through aryl magnesium[5c] and aryl lithium[12] additions onto silyl nitronates. When performed on nitromethylcycloalkenyl derivatives, the resulting oximes may be easily converted into fused isoxazoles under oxidative conditions.[13] We are currently exploring the potential of various catalysts to trigger the addition of boronic acids onto less reactive alkyl silylnitronate species.

Funding Information

M. D. K. thanks the Islamic Development Bank for a PhD fellowship. We thank the ENSTA Paris for financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690845.

References and Notes

(1) For reviews on boronic acids, see: (a) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2011**. (b) *Boron Reagents in Synthesis, ACS Symposium Series 1236*; Coca, A., Ed.; American Chemical Society: Washington DC, **2016**.

(2) For reviews on the Petassis reaction, see: (a) Candeias N. R.: Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169. (b) Ramadhar, T. R.; Batey, R. A. *Recent Advances in Nucleophilic Addition Reactions of Organoboronic Acids and their Derivatives to Unsaturated C–N Functionalities*, In *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2011**, Chap. 9, 427–477. (c) Guerrera, C. A.; Ryder, T. R. *The Petassis Borono-Mannich Multicomponent Reaction*, In *Boron Reagents in Synthesis, ACS Symposium Series 1236*; Coca, A., Ed.; American Chemical Society: Washington DC, **2016**, Chap. 9, 275–311.

(3) For a review, see: (a) Roscales, S.; Csakÿ, A. G. *Chem. Soc. Rev.* **2014**, *43*, 8215. For some recent examples, see: (b) Ortega, V.; del Castillo, E.; Csakÿ, A. G. *Org. Lett.* **2017**, *19*, 6236. (c) He, Z.; Song, F.; Sun, H.; Huang, Y. *J. Am. Chem. Soc.* **2018**, *140*, 2693. (d) Bomio, C.; Kabeshov, M. A.; Lit, A. R.; Lau, S.-H.; Ehlert, J.; Battilocchio, C.; Ley, S. V. *Chem. Sci.* **2017**, *8*, 6071.

(4) Candeias, N. R.; Veiros, L. F.; Afonso, C. A. M.; Gois, P. M. P. *Eur. J. Org. Chem.* **2009**, 1859.

(5) For a review on the Nef reaction, see: (a) Ballini, R.; Petrini, M. *Adv. Synth. Catal.* **2015**, *357*, 2371. For examples of nucleophilic additions leading to oximes, see: (b) Fanté, B.; Soro, Y.; Siaka, S.; Marrot, J.; Coustard, J.-M. *Synlett* **2014**, *25*, 969. (c) Fujisawa, T.; Kurita, Y.; Sato, T. *Chem. Lett.* **1983**, 1537. (d) Kim, J. N.; Song, J. H.; Ryu, E. K. *Synth. Commun.* **1995**, *25*, 1711. (e) Dumestre, P.; El Kaïm, L.; Grégoire, A. *Chem. Commun.* **1999**, 775.

(6) (a) Arndt, F.; Rose, J. D. *J. Chem. Soc.* **1935**, 1. (b) Kornblum, N. R.; Brown, A. *J. Am. Chem. Soc.* **1964**, *86*, 2681.

(7) Ono, N. *Alkylation, Acylation, and Halogenation of Nitro Compounds*, In *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, **2001**, Chap. 5, 126–158.

(8) For reviews, see: (a) *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis, 2nd ed*; Feuer, H., Ed.; John Wiley & Sons: New York, **2007**. (b) Weber, W. P. *Silyl Nitronates*, In *Silicon Reagents for Organic Synthesis. Reactivity and Structure Concepts in Organic Chemistry, Vol. 14*; Springer: Berlin/Heidelberg, **1983**.

(9) (a) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1982**, 551. (b) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Bull. Soc. Chim. Fr.* **1983**, 61. (c) Tamura, R.; Sato, M.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4368.

(10) (a) Maeda, K.; Hosokawa, T.; Murahashi, S. I.; Moritani, I. *Tetrahedron Lett.* **1973**, *14*, 5075. (b) Alberola, A.; Banez, J. M.; Calvo, L.; Rodriguez, M. T. R.; Sanudo, M. C. *J. Heterocycl. Chem.* **1993**, *30*, 467. (c) Zhu, X.; Wang, Y. F.; Ren, W.; Zhang, F. L.; Chiba, S. *Org. Lett.* **2013**, *15*, 3214. (d) Desai, V. G.; Naik, S. R.; Dhumaskar, K. L. *Synth. Commun.* **2014**, *44*, 1453. (e) Sun, Y.; Abdukader, A.; Zhang, H.; Yang, W.; Liu, C. *RSC Adv.* **2017**, *7*, 55786.

(11) **Typical Procedure: Preparation of 4a from 1a**
Et_3N (1.1 mmol, 0.15 ml) was added to a stirred solution of allylic nitro compound **1a** (1 mmol, 141 mg) and *tert*-butyldimethylsilyl chloride (1.1 mmol, 166 mg) in acetonitrile (2 mL). The reaction mixture was stirred for 30 min at room temperature and quickly filtered through a short column of silica gel, eluting with dichloromethane (100 mL) to give, after evaporation of the solvent, nitronate **2a** as a yellow oil formed in quantitative yield (256 mg, 1 mmol).
4-Ethylphenyl boronic acid (**3a**; 2 equiv, 1 mmol, 150 mg) was added to a solution of **2a** (1 equiv, 0.5 mmol, 128 mg) in acetonitrile (1 mL). After degassing with argon, the reaction mixture was heated at 70 °C under argon for 30 min. Evaporation of the solvent under reduced pressure followed by purification by flash chromatography on silica gel (PE/Et_2O, 100:0 to 80:20) afforded oxime **4a** as an orange solid (78 mg, 0.34 mmol, 68%); mp 161 °C; R_f = 0.35 (PE/Et_2O, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (br, 1 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 7.15 (d, *J* = 8.1 Hz, 2 H), 5.71–5.61 (m, 1 H), 2.70 (q, *J* = 7.6 Hz, 2 H), 2.39–2.29 (m, 2 H), 2.10–2.04 (m, 2 H), 1.71–1.54 (m, 4 H), 1.28 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.3, 144.4, 135.3, 135.0, 130.1, 128.7, 127.7, 28.8, 26.2, 24.7, 22.5, 22.2, 15.4. HRMS: *m/z* calcd for $C_{15}H_{19}NO$: 229.1467; found: 229.1464. IR (thin film): ν = 3214, 3038, 2932, 2866, 1551, 1447, 1262, 997, 968, 823, 737, 722 cm^{-1}.

(12) Colvin, E. W.; Robertson, A. D.; Seebach, D.; Beck, A. K. *J. Chem. Soc., Chem. Commun.* **1981**, 952.

(13) For more classical cycloaddition-based conversions of nitronate derivatives into isoxazoles, see: Namboothiri, I. N. N.; Rastogi, N. *Isoxazolines from Nitro Compounds: Synthesis and Applications, In Synthesis of Heterocycles via Cycloadditions, Vol. 12*; Gupta, R. R.; Hassner, A., Ed.; Springer: Berlin/Heidelberg, **2008**, 1–44.