DOI: 10.1002/adsc.201601378

Advanced Synthesis & Catalysis

Metal-Catalyzed Synthesis of Functionalized 1,2,4-Oxadiazoles from Silyl Nitronates and Nitriles

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Received: December 15, 2016; Revised: March 1, 2017; Published online: ■■ ■■, 0000

Supporting information for this article is available under http://dx.doi.org/10.1002/adsc.201601378.

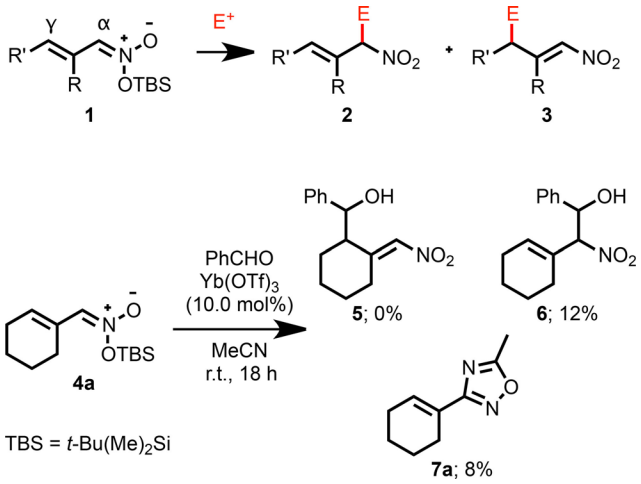
Abstract: The metal-catalyzed cycloaddition of silyl nitronates and nitriles leading to 1,2,4-oxadiazoles is described. Silver(I) triflate (AgOTf) and and ytterbium(III) triflate [Yb(OTf)$_3$] are suitable catalysts. A variety of functional groups is tolerated in the nitrile. The reaction works well for alkenyl and aryl silyl nitronates while the use of alkyl silyl nitronates is less efficient. Mechanistic studies are in favour of an elimination of *tert*-butyl(dimethyl)silanol (TBSOH) after the cycloaddition step. The new approach has also been applied for the synthesis of the drug ataluren.

Keywords: cycloaddition; heterocycles; homogeneous catalysis; 1,2,4-oxadiazoles; synthetic methods

Introduction

Silyl nitronates are versatile reagents[1,2] in organic synthesis, for example, for nitro-aldol reactions,[3] nitro-Michael reactions[4] and alkene-cycloadditions leading to isoxazolines.[5] Asymmetric nitro-aldol reactions using silyl nitronates have been achieved.[4,6] For β,γ-unsaturated silyl nitronates **1**, two possibilities exist *a priori* for the attack of an electrophile: α-attack leading to the β,γ-unsaturated product **2** or γ-attack giving the vinyl nitro compound **3** (Scheme 1).

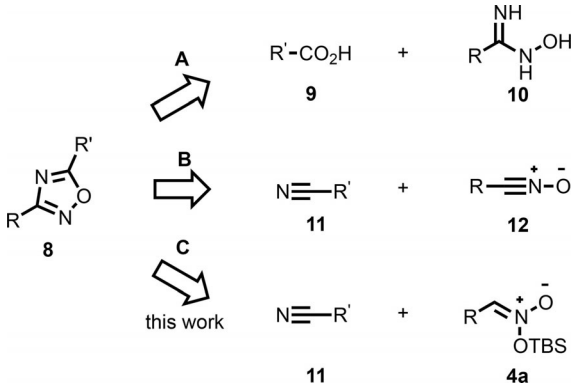
In order to address the possibility of a vinylogous nitro-aldol reaction, the β,γ-unsaturated silyl nitronate **4a**[7] was prepared. Interestingly, its reaction with benzaldehyde and Yb(OTf)$_3$ in acetonitrile did not provide any γ-attack product **5** but the α-attack product **6**, albeit only in low yield (Scheme 1). To our surprise an unexpected side product, the 1,2,4-oxadiazole **7a**, was isolated in low yield. The 1,2,4-oxadiazole was formed by a reaction of the silyl nitronate **4a** with the solvent acetonitrile. This observation prompted us to focus on this side reaction and to develop it into a novel, efficient synthesis for 1,2,4-oxadiazoles.



Scheme 1. Nitro-aldol reaction with a β,γ-unsaturated silyl nitronate and the unexpected formation of a 1,2,4-oxadiazole.

1,2,4-Oxadiazoles are frequently used substructures for multiple applications.[8] As stable bioisosteres for esters and amides, they are used as a valuable scaffold in medicinal chemistry[9] and crop protection.[10] The heteroaromatic ring system of 1,2,4-oxadiazoles can be part of functional organic materials.[11] Efficient synthetic methods to gain access to substituted 1,2,4-oxadiazoles are therefore important and numerous syntheses have been developed recently.[12,13] Most known synthetic approaches for 1,2,4-oxadiazoles **8** can be classified in two types (Scheme 2).

Path A describes the reaction of an activated carboxylic acid **9** and an amidoxime **10** or amidine.[14] Path B utilizes the addition of a nitrile **11** to a nitrile oxide **12**.[15] The present work communicates a novel path C to 1,2,4-oxadiazoles **8** using the metal-catalyzed addition of a nitrile **11** to a silyl nitronate **4**.



Scheme 2. Methods for the synthesis of 1,2,4-oxadiazoles.

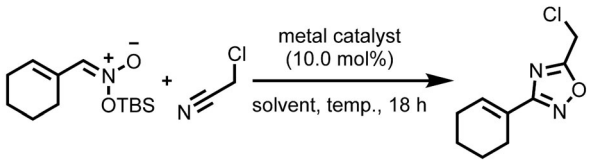
Results and Discussion

To optimize the novel path for the synthesis of 1,2,4-oxadiazoles various metal catalysts, solvents and reaction temperatures were screened. The studies were examined for the reaction of silyl nitronate **4a** and chloroacetonitrile **11b** to afford the 1,2,4-oxadiazole **7b** (Table 1). First, the necessity for the metal catalyst was tested (Table 1, entry 1). It could be shown that without the use of $Yb(OTf)_3$ the 1,2,4-oxadiazole did not form. Second, the amount of the nitrile was reduced from solvent to a stoichiometric quantity. Optimal results were obtained with three equivalents of nitrile.

Third, the role of the solvent on the reaction was investigated (Table 1, entries 2–6), which showed that non-polar solvents result in better yields (entries 2–4 and 7) while ethers (entries 5 and 6) and a green solvent such as 2-MeTHF are less suited (entry 8). Next, various metal catalysts were taken into consideration and tested. Most catalysts either showed lower yields (entries 9–11) or no product formation (entries 12–14). A Lewis acid such as $BF_3{\cdot}OEt_2$ afforded only 17% of the cycloadduct (entry 15). The use of AgOTf (entry 7) as a metal catalyst gave the 1,2,4-oxadiazole in improved yield. It was also possible to reduce the amount of metal catalyst from 10.0 mol% to 5.0 mol% (entry 17) without loss in yield. Further reduction to 2.0 mol% (entry 18) showed a slight decrease in yield and the optimization was therefore continued with 5.0 mol%. The reaction time of 18 h at room temperature could also be reduced to 1 h if the reaction was conducted at 100 °C (entry 19) with an additional increase in yield. A control experiment at 100 °C secured that no turnover of the starting material and no cycloaddition took place without a metal catalyst (entry 20).

With the optimized reaction conditions in hand our attention turned to the scope and functional group tolerance of the reaction. The substrate scope with respect to nitriles was explored first using the silyl nitronate **4a** as a reference (Table 2).

Table 1. Screening of metal catalysts, solvents, catalyst loading and temperature for the formation of 1,2,4-oxadiazole **7b**.



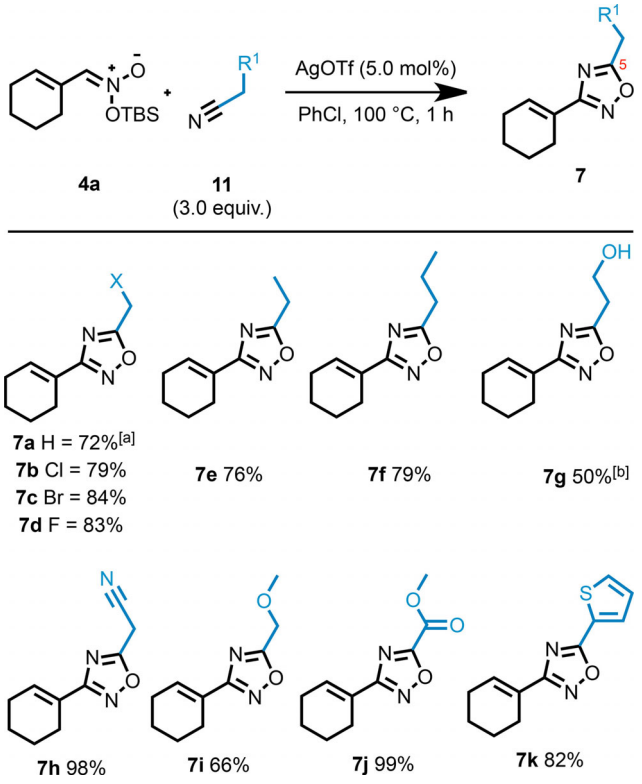
4a **11b** (3.0 equiv.) **7b**

Entry	Metal catalyst	Solvent	Temp. [°C]	Yield [%][a]
1	–	CH_2Cl_2	r.t.	–
2	$Yb(OTf)_3$	CH_2Cl_2	r.t.	48
3	$Yb(OTf)_3$	$PhCH_3$	r.t.	57
4	$Yb(OTf)_3$	PhCl	r.t.	63
5	$Yb(OTf)_3$	1,4-dioxane	r.t.	38
6	$Yb(OTf)_3$	THF	r.t.	31
7	AgOTf	PhCl	r.t.	72
8	AgOTf	2-MeTHF	80	42
9	$Cu(OTf)_2{\cdot}PhH$	PhCl	r.t.	56
10	$Sm(OTf)_3$	PhCl	r.t.	40
11	$Sc(OTf)_3$	PhCl	r.t.	36
12	ZnI_2	PhCl	r.t.	–
13	Co(I)[b]	PhCl	r.t.	–
14	$Bi(OTf)_3$	PhCl	r.t.	–
15[c]	$BF_3{\cdot}OEt_2$	PhCl	100	17
16[d]	AgOTf	PhCl	r.t.	68
17	AgOTf (5.0 mol%)	PhCl	r.t.	74
18	AgOTf (2.0 mol%)	PhCl	r.t.	70
19[c]	AgOTf (5.0 mol%)	PhCl	100	79
20	–	PhCl	100	–

[a] Isolated yield.
[b] Prepared by addition of Zn and ZnI_2 to $CoBr_2$(dppe).
[c] Reaction time 1 h instead of 18 h.
[d] 1.2 equiv. of chloroacetonitrile (**11b**).

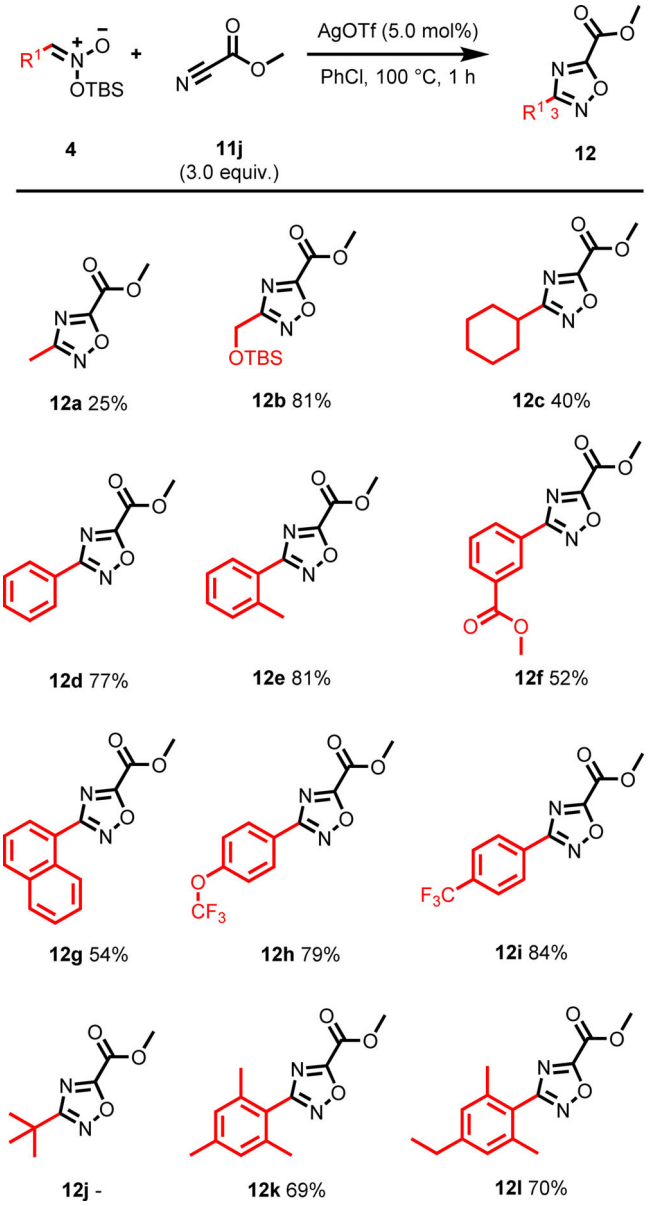
A variety of functional groups was tolerated. Remarkably, the successful use of halomethyl nitriles **11b–d** led to 1,2,4-oxadiazoles **7b–d** in very good yields (79–84%). The reaction was performed with an unprotected alcohol (**7g**, 50%) and a methyl ether (**7i**, 66%). The use of a di-nitrile such as malononitrile (**11h**) gave the mono-1,2,4-oxadiazole (**7h**, 98%) leaving the second nitrile group for further transformations. A methyl ester and a thiophene group were compatible with the reaction conditions and the desired cycloaddition products were obtained in excellent yields (**7j**, 99%; **7k**, 82%). In case of the low boiling acetonitrile, the amount of nitrile had to be increased (**7a**, 72%) other alkanenitriles could also be converted to the corresponding oxadiazoles in good yields (**7e**, 76% and **7f**, 79%). Performing the cycloaddition with cyanamide gave no oxadiazole product.

Table 2. Functional group screening on position 5 with cyclohexenyl silyl nitronate **4a** using various functionalized nitrile components **11a–k**. All yields are of isolated products.



[a] 30.0 equiv. of the nitrile were used.
[b] Reaction time of 18 h instead of 1 h.

Table 3. Screening to examine the influence of the residue in the α-position of the silyl nitronate on the cycloaddition.[a]



[a] All yields are of isolated products.

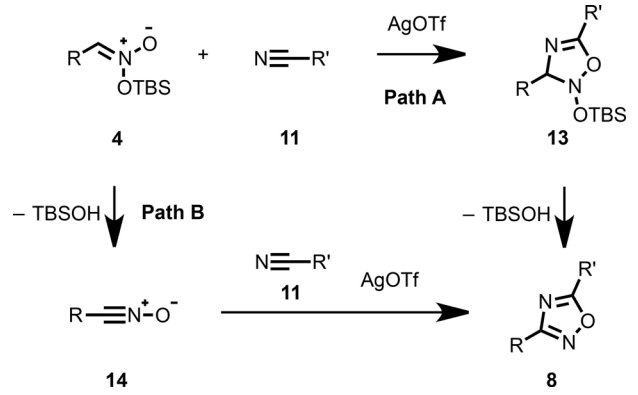
To further examine the scope and limitations of the reaction, several silyl nitronates **4a–l** were investigated under the optimized reaction conditions (Table 3). Methyl cyanoformate (**11j**) was used as a reference compound for these studies.

Silyl nitronates with an sp^2-carbon α to the nitrile (alkenyl, aryl) gave 1,2,4-oxadiazoles in good yields (**12d–i**) whereas silyl nitronates with an sp^3-carbon and a proton in the α-position gave the corresponding 1,2,4-oxadiazole in lower yields only (**12a**, **b** and **c**). For these cases, decomposition of the silyl nitronate to the nitroalkane was observed as a side reaction. No cycloadduct **12j** was formed in the reaction of *tert*-butyl silyl nitronate. The mesityl silyl nitronate **4k** and its derivative **4l** gave the corresponding 1,2,4-oxadiazoles **12k** and **12l** in good yields.

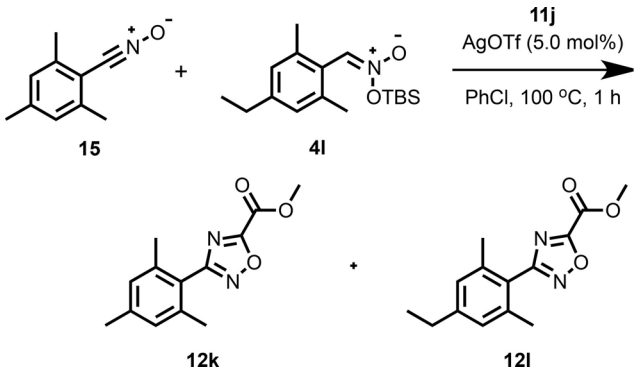
From a mechanistic point of view the reaction of a silyl nitronate **4** and a nitrile **11** to the oxadiazole **8** can proceed *via* two pathways A and B (Scheme 3): Path A consists of the Ag-catalyzed cycloaddition to the oxadiazoline **13** and subsequent thermal TBSOH-elimination to the oxadiazole **8**; path B includes the elimination of the silyl nitronate **4** to the nitrile oxide **14** and subsequent Ag-catalyzed cycloaddition with the nitrile **11** to yield **8**.

In a competition experiment 1.0 equiv. of mesitylnitrile oxide (**15**)[16] and 1.0 equiv. of silyl nitronate **4l** were allowed to react with 1.0 equiv. of nitrile **11j** (Scheme 4). GC reaction monitoring showed that both oxadiazoles **12k** and **12l** were formed in equal amounts, which indicates that both paths A and B are possible.

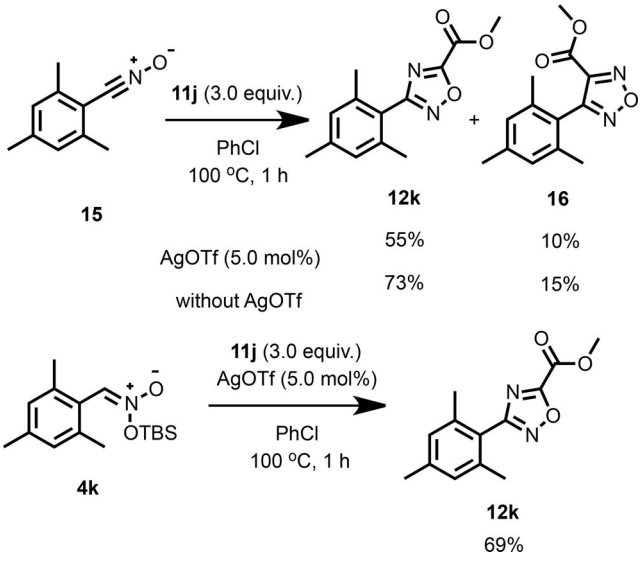
Further mechanistic insights came from studies on the regioselectivity of the cycloaddition reaction (Scheme 5). The reaction of the nitrile oxide **15** with the nitrile **11j** with or without AgOTf gave a mixture of both regioisomers, the 1,2,4-oxadiazole **12k** and the 1,2,3-oxadiazole **16**, with **12k** as the main product. In



Scheme 3. Mechanistic alternatives for 1,2,4-oxadiazole formation.



Scheme 4. Nitrile oxide *versus* silyl nitronate competition.

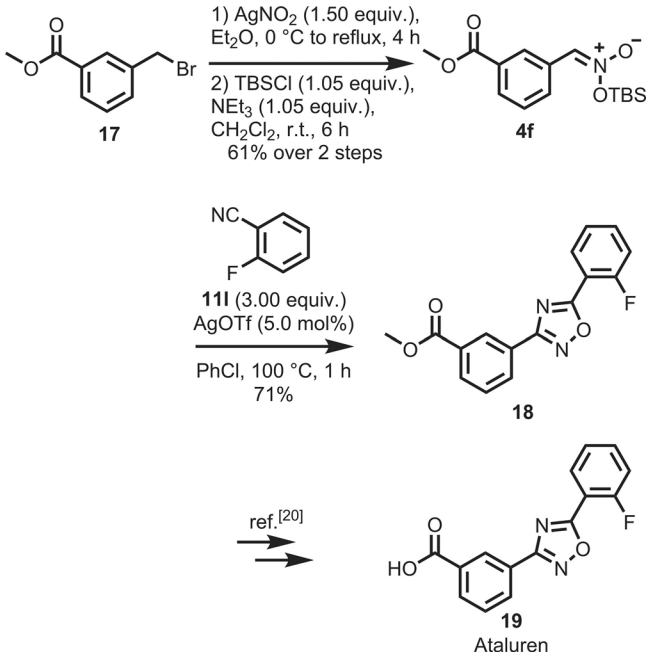


Scheme 5. Regioselectivity in the cycloaddition of nitrile oxide *versus* silyl nitronate.

contrast, the reaction of the silyl nitronate **4k** with the nitrile **11j** gave the 1,2,4-oxadiazole **12k** as the only cycloadduct. No other regioisomers were observed for all cases described in Table 2 and Table 3. The results of the regioselectivity studies point to path A as the favored reaction pathway.

Silver(I) as catalyst can coordinate and activate the nitrile and the silyl nitronate as well. Noteworthy is the difference of the Ag-mediated oxadiazole formation described here to the Pt(IV)-mediated reaction of cyclic nitronates and alkyl nitriles, where no cycloaddition had occurred.[17]

Ataluren (**19**) is a drug used for patients with nonsense-mutation-mediated cystic fibrosis and Duchenne muscular dystrophy.[18] The 1,2,4-oxadiazole core prompted us to apply our new method to the synthesis of ataluren (Scheme 6). Starting from the bromide **17**, the silyl nitronate **4f** was prepared *via* the corresponding nitroalkane[19] in 61% yield over 2 steps. Following the optimized procedure, the silyl nitronate **4f** was treated with AgOTf and nitrile **11l** to yield the 1,2,4-oxadiazole **18**. The hydrolysis of the methyl ester **18** to atularen **19** has already been reported.[20]



Scheme 6. Synthesis of ataluren precursor **18**.

Conclusions

In conclusion, we have developed a novel synthesis of 1,2,4-oxadiazoles from silyl nitronates and nitriles. The reaction is catalyzed by $Yb(OTf)_3$ and AgOTf. Good yields were obtained with alkenyl and aryl silyl nitronates while the use of alkyl nitronates remains a subject for future improvements. Mechanistic studies indicate that the silyl nitronate/nitrile cycloaddition step is followed by the elimination of TBSOH to deliver the 1,2,4-oxadiazole. In contrast to the known nitrile oxide/nitrile cycloaddition method, the present

silyl nitronate/nitrile cycloaddition method exhibits a better regioselectivity and broader functional group tolerance.

Experimental Section

General Procedure (GP1) for the Synthesis of Silyl Nitronates

To a solution of TBSCl (1.05 equiv.) and the nitro compound (1.00 equiv.) in CH_2Cl_2 was added at room temperature in one portion triethylamine (1.05 equiv.) and the reaction mixture was stirred for 4 h. The reaction mixture was diluted with pentane and filtered twice over Celite®. The silyl nitronate could be obtained after removal of the solvent under reduced pressure.

All silyl nitronates were stored in a freezer for better preservation.

General Procedure (GP2) for the Synthesis of 1,2,4-Oxadiazoles from Silyl Nitronates and Nitriles

To a solution of the nitrile (3.0 equiv.) and AgOTf (5.0 mol%) in PhCl was added the silyl nitronate (1.0 equiv.) in one portion. The solution was stirred generally for 1 h (monitored by TLC) at 100 °C. After cooling to room temperature the solvent was removed under reduced pressure. Column chromatography on silica gel (pentane:EtOAc) gave the 1,2,4-oxadiazole product.

***tert*-Butyldimethylsilyl cyclohexenemethyleneazinate (4a):** The silyl nitronate **4a** was prepared according to **GP1** from 1-(nitromethyl)-1-cyclohexene[21] (6.30 g, 44.6 mmol, 1.00 equiv.), TBSCl (7.06 g, 46.8 mmol, 1.05 equiv.) and triethylamine (6.53 mL, 46.8 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure the product was obtained as yellow crystals; yield: 10.1 g (39.2 mmol, 89%).

***tert*-Butyldimethylsilyl ethylideneazinate (4b):** The silyl nitronate **4b** was prepared according to **GP1** from nitroethane (2.00 mL, 27.9 mmol, 1.00 equiv.), TBSCl (4.43 g, 29.4 mmol, 1.05 equiv.) and triethylamine (4.10 mL, 29.4 mmol, 1.05 equiv.). After filtration over Celite®, evaporation of the solvent under reduced pressure and distillation (70 °C/7.0 mbar) the product was obtained as colourless oil which crystallized in a freezer; yield: 4.54 g (24.0 mmol, 86%).

***tert*-Butyldimethylsilyl-2-(*tert*-butyldimethylsiloxy)ethylideneazinate (4c):** The silyl nitronate **4c** was prepared according to **GP1** from nitroethanol (0.920 g, 9.79 mmol, 1.00 equiv.), TBSCl (3.10 g, 20.6 mmol, 2.10 equiv.) and triethylamine (2.85 mL, 20.6 mmol, 2.10 equiv.). After filtration over Celite®, evaporation of the solvent under reduced pressure and bulb to bulb distillation the product was obtained as a white solid; yield:2.27 g (7.11 mmol, 73%).

***tert*-Butyldimethylsilyl cyclohexylmethyleneneazinate (4d):** The silyl nitronate **4d** was prepared according to **GP1** from nitromethylcyclohexane[22] (0.618 g, 4.32 mmol, 1.00 equiv.), TBSCl (0.683 g, 4.53 mmol, 1.05 equiv.) and triethylamine (0.63 mL, 4.53 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure the product was obtained as a yellow oil which crystallized in a freezer; yield: 1.11 g (4.31 mmol, 99%).

***tert*-Butyldimethylsilyl phenylmethyleneazinate (4e):** The silyl nitronate **4e** was prepared according to **GP1** from 1-nitro-1-phenylmethane[23] (0.617 g, 4.49 mmol, 1.00 equiv.), TBSCl (0.712 g, 4.72 mmol, 1.05 equiv.) and triethylamine (0.66 mL, 4.72 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure the product was obtained as yellow oil which crystallized in a freezer; yield: 0.762 g (3.03 mmol, 67%).

***tert*-Butyldimethylsilyl 2-methylphenylmethyleneazinate (4f):** The silyl nitronate **4f** was prepared according to **GP1** from 2-methyl-(nitromethyl)benzene[19] (0.286 g, 1.98 mmol, 1.00 equiv.), TBSCl (0.299 g, 1.98 mmol, 1.05 equiv.) and triethylamine (0.201 mL, 1.98 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure the product was obtained as colourless oil; yield: 0.502 g (1.89 mmol, 99%).

***tert*-Butyldimethylsilyl 3-methylcarboxyphenylmethyleneazinate (4g):** The silyl nitronate **4g** was prepared according to **GP1** from 3-methylcarboxy-(nitromethyl)benzene (0.165 g, 0.845 mmol, 1.00 equiv.), TBSCl (0.134 g, 0.888 mmol, 1.05 equiv.) and triethylamine (0.12 mL, 0.888 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure was the product obtained as a white solid; yield: 0.234 g (0.755 mmol, 89%).

***tert*-Butyldimethylsilyl 2-napthalenemethyleneazinate (4h):** The silyl nitronate **4h** was prepared according to **GP1** from 2-(nitromethyl)naphthalene[24] (0.075 g, 0.401 mmol, 1.00 equiv.), TBSCl (0.063 g, 0.421 mmol, 1.05 equiv.) and triethylamine (0.06 mL, 0.421 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure the product was obtained as a white solid; yield: 0.119 g (0.393 mmol, 98%).

***tert*-Butyldimethylsilyl 4-trifluoromethoxybenzenemethyleneazinate (4i):** The silyl nitronate **4i** was prepared according to **GP1** from 4-trifluoromethoxy-(nitromethyl)benzene[19] (0.175 g, 0.794 mmol, 1.00 equiv.), TBSCl (0.126 g, 0.834 mmol, 1.05 equiv.) and triethylamine (0.12 mL, 0.844 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure was the product obtained as a colourless solid; yield: 0.237 g (0.707 mmol, 89%).

***tert*-Butyldimethylsilyl 4-trifluoromethylphenylmethyleneazinate (4j):** The silyl nitronate **4j** was prepared according to **GP1** from 4-trifluoromethyl-(nitromethyl)benzene[19] (0.115 g, 0.561 mmol, 1.00 equiv.), TBSCl (0.088 g, 0.589 mmol, 1.05 equiv.) and triethylamine (0.08 mL, 0.589 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure the product was obtained as a white solid; yield: 0.169 g (0.531 mmol, 95%).

***tert*-Butyldimethylsilyl 2,4,6-trimethylphenylmethyleneazinate (4k):** 1,3,5-Trimethyl-2-(nitromethyl)benzene was prepared by adding a suspension of urea hydrogen peroxide (UHP) (6.05 g, 64.3 mmol, 21.0 equiv.) in CH_3CN (40 mL) dropwise at 0 °C to a solution of trifluoroacetic anhydride (TFAA) (8.10 mL, 58.2 mmol, 19.0 equiv.) in CH_3CN (7.0 mL). The mixture was stirred 30 min and afterwards added to a suspension of Na_2HPO_4 (10.9 g, 61.3 mmol, 20.0 equiv.) and 2,4,6-trimethylbenzaldehyde oxime[16]

(0.50 g, 3.06 mmol, 1.00 equiv.) in CH_3CN (8.0 mL) at 0 °C. After stirring for 18 h the amount of solvent was reduced. The remaining participate was dissolved in aqueous saturated $NaHCO_3$ (30.0 mL), extracted with Et_2O (3×20.0 mL) and dried over Na_2SO_4. Column chromatography on silica gel (pentand:EtOAc; 9:1) gave the product as a yellow liquid; yield: 0.288 g (1.60 mmol, 53%).

The silyl nitronate **4k** was prepared according to **GP1** from 1,3,5-trimethyl-2-(nitromethyl)benzene (0.246 g, 1.37 mmol, 1.00 equiv.), TBSCl (0.217 g, 1.44 mmol, 1.05 equiv.) and triethylamine (0.20 mL, 1.44 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure the product was obtained as yellow oil; yield: 0.364 g (1.23 mmol, 90%).

***tert*-Butyldimethylsilyl 2,6-dimethyl-4-methylphenylmethyleneazinate (4l):** To a suspension of methyl 4-bromo-2,6-dimethylbenzoate (0.263 g, 1.08 mmol, 1.00 equiv.), Cs_2CO_3 (1.06 g, 3.25 mmol, 3.00 equiv.), Pd(dppf)Cl_2 (0.016 g, 0.022 mmol, 2.0 mol%) in THF (2.0 mL, red mixture) was added triethylborane (1 M in THF, 3.25 mL, 3.25 mmol, 3.00 equiv.) in one portion at room temperature (brown mixture). The mixture was refluxed (70 °C) for 1 h (beige mixture). After cooling to room temperature the mixture was washed with water (10.0 mL), extracted with Et_2O (3× 15.0 mL) and dried over Na_2SO_4. Column chromatography on silica gel (pentane:MTBE; 5:1) gave the product methyl 4-ethyl-2,6-dimethylbenzoate as a yellow liquid; yield: 0.206 g (1.07 mmol, 99%).

To a solution of methyl 4-ethyl-2,6-dimethylbenzoate (0.205 g, 1.07 mmol, 1.00 equiv.) in Et_2O (5.0 mL) was added at 0 °C in small portions $LiAlH_4$ (0.045 g, 1.17 mmol, 1.10 equiv.) and the mixture was stirred for 1 h. Afterwards the reaction mixture was quenched with water (10.0 mL), extracted with Et_2O (3×20.0 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the alcohol as a white solid; yield: 0.176 g (1.07 mmol, quant.).

PPh_3 (0.324 g, 1.24 mmol, 1.20 equiv.) and NBS (0.219 g, 1.24 mmol, 1.20 equiv.) were dissolved in CH_2Cl_2 (3.0 mL) in a separate flask at 0 °C and stirred under an argon atmosphere for 5 min at room temperature (orange solution). The mixture was then added to the alcohol from above (0.169 g, 1.03 mmol, 1.00 equiv.) in CH_2Cl_2 (2.0 mL) at room temperature and stirred for 1.5 h (solution turned to a dark violet colour). All volatile compounds were removed under reduced pressure and column chromatography on silica gel (pentane:MTBE; 10:1) gave the bromide as a colourless solid; yield: 0.172 g (0.757 mmol, 74%).

To a solution of silver nitrite (0.129 g, 0.837 mmol, 1.55 equiv.) in Et_2O (3.0 mL) was added a solution of the above benzyl bromide (0.123 g, 0.540 mmol, 1.00 equiv.) in Et_2O (2.0 mL) at 0 °C (flask covered with tin foil). The solution was stirred at this temperature for 1 h and afterwards heated to reflux (45 °C) for 4 h. The mixture was cooled to room temperature and filtered over Celite® using EtOAc as a eluent. Column chromatography on silica gel (pentane:EtOAc; 20:1) gave the nitro compound as a white solid; yield: 0.054 g (0.279 mmol, 52%).

The silyl nitronate **4l** was prepared according to **GP1** from 5-ethyl-1,3-dimethyl-2-(nitromethyl)benzene (0.054 g, 0.279 mmol, 1.00 equiv.), TBSCl (0.044 g, 0.0293 mmol, 1.05 equiv.) and triethylamine (0.04 mL, 0.293 mmol, 1.05 equiv.). After filtration over Celite® and evaporation of the solvent under reduced pressure the product was obtained as a yellow oil; yield: 0.084 g (0.272 mmol, 97%).

3-(Cyclohexen-1-yl)-5-methyl-1,2,4-oxadiazole (7a): The 1,2,4-oxadiazole **7a** was prepared according to **GP2** from acetonitrile (**11a**, 1.56 mL, 30.0 mmol, 1.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a yellow oil; yield: 0.118 g (0.717 mmol, 72%).

3-(Cyclohexen-1-yl)-5-(chloromethyl)-1,2,4-oxadiazole (7b): The 1,2,4-oxadiazole **7b** was prepared according to **GP2** from chloroacetonitrile (**11b**, 0.20 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 20:1) as a colourless oil; yield: 0.156 g (0.789 mmol, 79%).

3-(Cyclohexen-1-yl)-5-(bromomethyl)-1,2,4-oxadiazole (7c): The 1,2,4-oxadiazole **7c** was prepared according to **GP2** from bromoacetonitrile (**11c**, 0.22 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a colourless oil; yield: 0.205 g (0.841 mmol, 84%).

3-(Cyclohexen-1-yl)-5-(fluoromethyl)-1,2,4-oxadiazole (7d): The 1,2,4-oxadiazole **7d** was prepared according to **GP2** from fluoroacetonitrile (**11d**, 0.17 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a colourless liquid; yield: 0.151 g (0.830 mmol, 83%).

3-(Cyclohexen-1-yl)-5-ethyl-1,2,4-oxadiazole (7e): The 1,2,4-oxadiazole **7e** was prepared according to **GP2** from propionitrile (**11e**, 0.22 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 20:1) as a yellow liquid; yield: 0.136 g (0.763 mmol, 76%).

3-(Cyclohexen-1-yl)-5-propyl-1,2,4-oxadiazole (7f): The 1,2,4-oxadiazole **7f** was prepared according to **GP2** from butyronitrile (**11f**, 0.26 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 20:1) as a yellow liquid; yield: 0.152 g (0.792 mmol, 79%).

3-(Cyclohexen-1-yl)-5-(2-hydroxyethyl)-1,2,4-oxadiazole (7g): The 1,2,4-oxadiazole **7g** was prepared according to **GP2** from 3-hydroxypropionitrile (**11g**, 0.21 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 1:1) as a colourless liquid; yield: 0.098 g (0.503 mmol, 83%).

3-(Cyclohexen-1-yl)-5-(cyanomethyl)-1,2,4-oxadiazole (7h): The 1,2,4-oxadiazole **7h** was prepared according to **GP2** from malononitrile (**11h**, 0.051 g, 0.775 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.066 g, 0.258 mmol, 1.00 equiv.) in chlorobenzene (1.3 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 5:1) as a brown solid; yield: 0.048 g (0.254 mmol, 98%).

3-(Cyclohexen-1-yl)-5-(methoxymethyl)-1,2,4-oxadiazole (7i): The 1,2,4-oxadiazole **7i** was prepared according to **GP2** from methoxyacetonitrile (**11i**, 0.23 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and the nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 5:1) as a yellow liquid; yield: 0.128 g (0.659 mmol, 66%).

Methyl 3-(cyclohexen-1-yl)-1,2,4-oxadiazole-5-carboxylate (7j): The 1,2,4-oxadiazole **7j** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.24 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a colourless solid; yield: 0.208 g (0.998 mmol, 99%).

3-(Cyclohexen-1-yl)-5-(thiophen-2-yl)-1,2,4-oxadiazole (7k): The 1,2,4-oxadiazole **7k** was prepared according to **GP2** from 2-cyanothiophene (**11k**, 0.28 mL, 3.00 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4a** (0.256 g, 1.00 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a colourless solid; yield: 0.191 g (0.822 mmol, 82%)

Methyl 3 -methyl-1,2,4-oxadiazole-5-carboxylate (12a): The 1,2,4-oxadiazole **12a** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.39 mL, 4.75 mmol, 3.00 equiv.), AgOTf (0.021 g, 5.0 mol%) and nitronate **4b** (0.300 g, 1.59 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a colourless solid; yield: 0.057 g (0.399 mmol, 25%).

Methyl 3-(*tert*-butyldimethylsilyloxymethyl)-1,2,4-oxadiazole-5-carboxylate (12b): The 1,2,4-oxadiazole **12b** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.30 mL, 3.76 mmol, 3.00 equiv.), AgOTf (0.016 g, 5.0 mol%) and nitronate **4c** (0.400 g, 1.25 mmol, 1.00 equiv.) in chlorobenzene (6.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 5:1) as a white solid; yield: 0.128 g (0.471 mmol, 38%).

Methyl 3-cyclohexyl-1,2,4-oxadiazole-5-carboxylate (12c): The 1,2,4-oxadiazole **12c** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.22 mL, 2.80 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4d** (0.240 g, 0.930 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a yellow oil; yield: 0.079 g (0.376 mmol, 40%).

Methyl 3-phenyl-1,2,4-oxadiazole-5-carboxylate (12d): The 1,2,4-oxadiazole **12d** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.26 mL, 3.57 mmol, 3.00 equiv.), AgOTf (0.013 g, 5.0 mol%) and nitronate **4e** (0.300 g, 0.477 mmol, 1.00 equiv.) in chlorobenzene (3.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a colourless solid; yield: 0.188 g (0.920 mmol, 77%).

Methyl 3-(2-methylphenyl)-1,2,4-oxadiazole-5-carboxylate (12e): The 1,2,4-oxadiazole **12e** was prepared according to **GP2** from methyl cyanoformate (**1j**, 0.15 mL, 1.81 mmol, 3.00 equiv.), AgOTf (0.008 g, 5.0 mol%) and nitronate **4f** (0.160 g, 0.603 mmol, 1.00 equiv.) in chlorobenzene (3.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a white solid; yield: 0.106 g (0.487 mmol, 80%).

Methyl 3-(3-methylcarboxyphenyl)-1,2,4-oxadiazole-5-carboxylate (12f): The 1,2,4-oxadiazole **12f** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.18 mL, 2.20 mmol, 3.00 equiv.), AgOTf (0.010 g, 5.0 mol%) and nitronate **4g** (0.227 g, 0.734 mmol, 1.00 equiv.) in chlorobenzene (3.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 5:1) as a colourless solid; yield: 0.095 g (0.383 mmol, 52%).

Methyl 3-naphthyl-1,2,4-oxadiazole-5-carboxylate (12g): The 1,2,4-oxadiazole **12g** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.06 mL, 0.746 mmol, 3.00 equiv.), AgOTf (0.003 g, 5.0 mol%) and the nitronate **4h** (0.075 g, 0.249 mmol, 1.00 equiv.) in chlorobenzene (1.5 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a yellow solid; yield: 0.034 g (0.134 mmol, 54%).

Methyl 3-(4-trifluoromethoxy)phenyl-1,2,4-oxadiazole-5-carboxylate (12h): The 1,2,4-oxadiazole **12h** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.11 mL, 1.43 mmol, 3.00 equiv.), AgOTf (0.006 g, 5.0 mol%) and nitronate **4i** (0.160 g, 0.477 mmol, 1.00 equiv.) in chlorobenzene (3.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 10:1) as a colourless solid; yield: 0.108 g (0.375 mmol, 79%).

Methyl 3-(4-trifluoromethyl)phenyl-1,2,4-oxadiazole-5-carboxylate (12i): The 1,2,4-oxadiazole **12i** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.10 mL, 1.27 mmol, 3.00 equiv.), AgOTf (0.006 g, 5.0 mol%) and nitronate **4j** (0.135 g, 0.423 mmol, 1.00 equiv.) in chlorobenzene (2.3 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 5:1) as a white solid; yield: 0.096 g (0.354 mmol, 84%).

3-(2,4,6-Trimethylphenyl)-1,2,4-oxadiazole-5-carboxylate (12k): The 1,2,4-oxadiazole **12k** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.07 mL, 0.913 mmol, 3.00 equiv.), AgOTf (0.004 g, 5.0 mol%) and nitronate **4l** (0.089 g, 0.304 mmol, 1.00 equiv.) in chlorobenzene (2.5 mL). The solution was stirred for 1 h at 100 °C and the product

could be obtained after column chromatography on silica gel (pentane:EtOAc; 5:1) as a white solid; yield: 0.052 g (0.212 mmol, 69%).

Methyl 3-(2,6-Dimethyl-4-ethylphenyl)-1,2,4-oxadiazole-5-carboxylate (12l): The 1,2,4-oxadiazole **12l** was prepared according to **GP2** from methyl cyanoformate (**11j**, 0.06 mL, 0.782 mmol, 3.00 equiv.), AgOTf (0.004 g, 5.0 mol%) and nitronate **4m** (0.080 g, 0.261 mmol, 1.00 equiv.) in chlorobenzene (1.5 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 5:1) as a colourless liquid; yield: 0.047 g (0.182 mmol, 70%).

Methyl 3-[5-(2fluorophenyl)-1,2,4-oxadiazol-3-yl]benzoate (18): The 1,2,4-oxadiazole **18** was prepared according to **GP2** from 2-fluorobenzonitrile (**11l**, 0.21 mL, 1.94 mmol, 3.00 equiv.), AgOTf (0.008 g, 5.0 mol%) and the nitronate **4g** (0.200 g, 0.647 mmol, 1.00 equiv.) in chlorobenzene (5.0 mL). The solution was stirred for 1 h at 100 °C and the product could be obtained after column chromatography on silica gel (pentane:EtOAc; 15:1) as a white solid; yield: 0.138 g (0.462 mmol, 71%).

Competition eExperiment (Scheme 4): Nitrile Oxide 15 *versus* Silyl Nitronate 4l

The competition experiment was carried out according to **GP2** with methyl cyanoformate (**11j**, 10.0 μL, 0.065 mmol, 1.00 equiv.), AgOTf (0.9 mg, 5.0 mol%), the nitrile oxide **15** (0.010 g, 0.065 mmol, 1.00 equiv.) and the silyl nitronate **4l** (0.020 g, 0.065 mmol, 1.00 equiv.) in chlorobenzene (0.40 mL). The reaction mixture was stirred for 1 h at 100 °C and monitored by GC. Oxadiazole **12k** (R_t = 15.03 min; 40%), oxadiazole **12l** (R_t = 15.27 min; 46%) and oxadiazole **16** (R_t = 15.53 min; 13%) were formed.

Regioselectivity Studies (Scheme 5): Nitrile Oxide 15 with Cyanomethyl Ester 11j

The 1,2,4-oxadiazole **12k** and 1,2,3-oxadiazole **16** were prepared according to **GP2** from methyl cyanoformate (**11j**, 0.15 mL, 1.86 mmol, 3.00 equiv.), AgOTf (0.008 g, 5.0 mol%) and nitrile oxide **15** (0.100 g, 0.620 mmol, 1.00 equiv.) in chlorobenzene (3.0 mL). The solution was stirred for 1 h at 100 °C and the products could be obtained as a mixture (**12k** and **16**) after column chromatography on silica gel (pentane:EtOAc; 5:1) as a colourless solid; yield: 0.098 g (0.398 mmol, 64%).

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft is greatfully acknowledged.

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