JOC The Journal of Organic Chemistry

Freie Universität Berlin

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J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 28 Apr 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Fe(II)/Au(I) Relay Catalyzed Propargylisoxazole to Pyridine Isomerization: Access to 6-Halonicotinates

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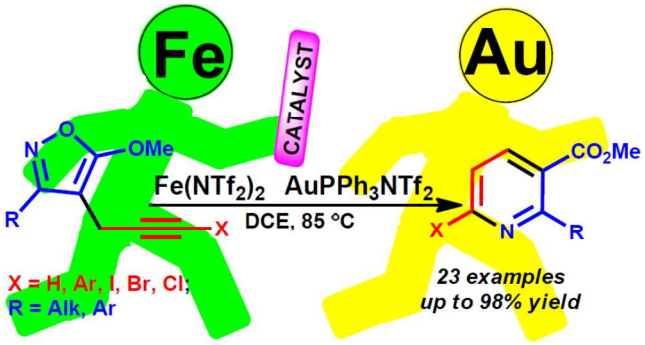
KEYWORDS: gold, homogeneous catalysis, iron, isoxazole, pyridine.



ABSTRACT: An efficient synthesis of methyl nicotynates/6-halonicotinates by the domino isomerization of 4-propargyl/(3-halopropargyl)-5-methoxyisoxazoles under Fe(II)/Au(I) relay catalysis was developed. It was found that $FeNTf_2$ is effective catalyst for first step of the domino isomerization, transformation of isoxazole to 2*H*-azirine, which is compatible with $Ph_3PAuNTf_2$, catalyzing the second step.

INTRODUCTION

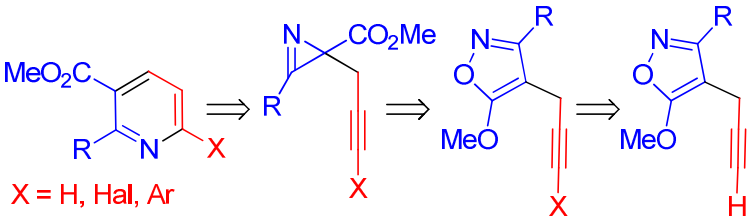
Pyridine is one of the most important nitrogen heterocycles found in natural products, is widely exploited in pharmaceutical and agrochemistry, and industry. This has led to the development a plethora of methods for their preparation. Nevertheless new synthetic strategies, based on recent developments in organic synthesis, still need to be explored[1] due to, in particular, all increasing use of pyridine derivatives as ligands.[2] 2-Halopyridines are important building blocks for synthesis of both pyridine derivatives and diverse pyridine-containing heterocycles via cross-coupling reactions.[3, 4] Preparation of 2-halopyridines by direct halogenation of substituted pyridines suffers from poor regioselectivity and low reactivity of pyridine core.[5] Halogenation of pyridine N-oxides with phosgene, POX_3, SOX_2 and other halogenating agents is used more successfully; however the problem of selectivity and using harsh reaction conditions are often characteristic of this approach too.[6] The examples of the formation of 2-halopyridine derivative from acyclic precursor, which are rare and very specific, are represented by the cyclization of 3-amino-5-aryl-2,4-dicyanopenta-2,4-dienimidoyl bromide/chloride and 1-alkyl-4-amino-4-bromo/chloro-1-oxobut-3-ene-2,2,3-tricarbonitrile providing 6-aryl-4-amino-2-halopyridine-3,5-dicarbonitriles and methyl 6-alkyl-3-cyano-2-halopyridine-4-carboxylates.[7] Three approaches to 2-halopyridines involving the formation of two bonds of the pyridine ring were also reported. In the first two, the C2-C3 and C4-C5 bonds of the pyridine system were formed via a two-step procedure involving Diels-Alder reaction of halogenated 1,2,4-triazines[8] or 2*H*-1,4-oxazine-2-ones[8f, 9] with unsaturated compounds followed by nitrogen or carbon dioxide extrusion. The complementary approach via Diels-Alder reaction of chlorophenylacetylene with methyl 3-((trimethylsilyl)oxy)-2-(((trimethylsilyl)oxy)imino)but-3-enoate is not effective, leading to the mixture of the corresponding 2- and 3-chloropyridines.[10] Coupling of acetylenes, nitriles, and Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl leads to azatitanacyclopentadienes reacting with sulfonylacetylenes with formation of pyridyltitanium compounds, which give 2-iodo-substituted pyridines in moderate yield by reaction with iodine.[11]

One of the most promising contemporary technics for the construction of molecular frameworks in a resource-efficient and sustainable manner is relay multicatalysis.[12] Despite the incredible potential of this synthetic approach it still has rare been utilized for the formation a pyridine nucleus. Possible reasons for this are necessity of orthogonal reactivity of catalysts and compatibility of every reaction component with a specific set of reaction conditions. The following works, where pyridine derivatives were obtained under relay catalytic conditions, were published.[13-16] Tetrahydropyridine derivatives were prepared utilizing an asymmetric organocatalytic nitro-Mannich reaction of 5-nitropent-1-ynes with protected aldimines followed by a gold-catalyzed alkyne hydroamination/isomerization sequence.[13] Functionalized 1,2-dihydroisoquinolines were synthesized by reaction of 2-alkynylbenzaldehyde, aniline and α,β-unsaturated ketone under metal (AgOTf) and organo (PPh_3) catalysis.[14] Enantioselective [4+2]-cycloaddition reaction catalyzed by chiral phosphoric acid and a subsequent catalytic intramolecular hydroamination by gold(I) complex provides access to julolidine derivatives starting from 2-propargylanilines, aldehydes and enamine.[15] 4-Substituted 1,2-dihydroquinoline derivatives were prepared via indium-catalyzed intramolecular hydroarylation of 2-(bromopropargyl)anilines followed by palladium-catalyzed cross-coupling reaction using triorganoindium reagents.[16]

Recently Gagosz *et al*. discovered the effective gold-catalyzed transformation of alkyl 2-propargyl-2*H*-azirine-2-carboxylates to functionalized pyridines.[17] Isoxazoles under certain conditions can be transformed into 2-carbonyl-substituted 2*H*-azirines, and this isomerization can serve as a reactivity switch that enables easier manipulation with substituents in an isoxazole, which is usually much less reactive than an azirine counterpart.[18] Taking all this into account and based on our experience in use of isoxazoles as synthetic equivalent of 2*H*-azirines,[19] we postulated that the use of propargyl-substituted isoxazoles in combination with an appropriate catalytic system could allow easy direct access to pyridine derivatives, and in particular, highly synthetically useful 2-halopyridines. Retrosynthetic scheme for the synthesis of nicotynates/6-halonicotinates from C-

propargylated keto esters involves isoxazole-azirine/azirine-pyridine isomerization cascade as the key step of the synthetic sequence (Scheme 1). The advantages of this scheme are that it allows (a) the late-stage functionalization of the acetylenic moiety, and (b) avoiding working with unstable azirines when implementing a domino variant of the isoxazole-pyridine isomerization.

In this communication, we wish to report the synthesis of pyridines, including 2-halopyridines, by the domino reaction of isoxazoles under Fe(II)/Au(I) relay catalysis (Scheme 1).



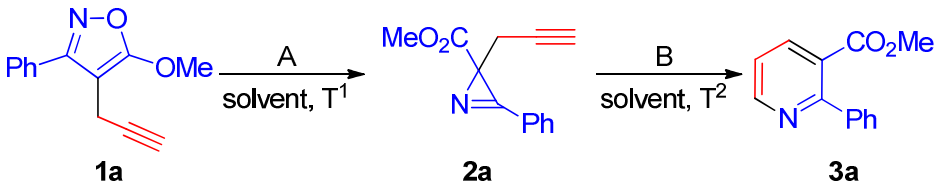
Scheme 1. Retrosynthetic scheme for the synthesis of nicotinates from isoxazoles.

RESULTS AND DISCUSSION

At first we examined whether isoxazole **1a** can undergo thermal conversion into pyridine **3a**, but only the starting material was found in the reaction mixture even after heating at high temperature (Table 1, Entry 1). We decided, therefore, to check the ability of some metal salts and complexes, which catalyze isomerization of 5-alkoxyisoxazole to 2*H*-azirine-2-carboxylate,[18] to induce the subsequent conversion of azirine **2a** to nicotinate **3a**. Iron(II) chloride is well known to promote the isoxazole-azirine transformation,[18-20] and it was, therefore, not unexpected to obtain azirine **2a** in a nearly quantitative yield under reaction of isoxazole **1a** at ambient temperature for 2 h (Table 1, Entry 2), no other products were, however, detected in the reaction mixture even upon longer heating at elevated temperature (Table 1, Entry 3). The similar result was obtained with molybdenum hexacarbonyl, which was used as promoter of the 2*H*-azirine–isoxazole interconversion (Table 1, Entry 4).[18, 21] Copper(I) NHC complex (IPrCuCl), which was reported as catalyst for N-$C_{(2)}$ azirine bond cleavage,[22] showed ability to catalyze both the isomerization of isoxazole **1a** to azirine **2a**, and the formation of nicotinate **3a**, although in lesser extent (Table 1,

Entry 5). We observed only a resignification of isoxazole **1a** under the reaction conditions, which were used for transformation of 2-allyl-2*H*-azirines to pyridines promoted by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[23] (Table 1, Entry 6). However addition of DBU to the reaction mixtures containing azirine **2a**, which was formed from isoxazole **1a** under metal catalysis, afforded nicotinate **3a** in moderate yields (Table 1, Entries 7-9). Isoxazole **1a** remained intact under heating in the presence of Au-complexes (Table 1, Entries 10-12), although it was reported that isoxazoles react under gold-catalysis with ynamides giving substituted pyrroles.[24] Refluxing azirine **2a** in 1,2-dichloroethane (DCE) in the presence of catalytic amount of $Rh_2(OAc)_4$, AgOTf, Ph_3PAuCl showed no reaction, whereas in the presence of $ZnBr_2$ and $Ph_3PAuNTf_2$ 32 and 90%, respectively, of nicotinate **3a** was formed. These experiments revealed that two different catalysts are required to transform isoxazole **1a** to nicotinate **3a**: (1) for isomerization of isoxazole **1a** to azirine **2a**, most probably derivatives of Fe(II) and (2) for isomerization of azirine **2a** to nicotinate **3a**, most probably derivatives of Au(I). Addition of $PhPAuNTf_2$ to the reaction mixture containing azirine **2a,** formed under the $FeCl_2 \cdot 4H_2O$ catalyzed isomerization of **1a**, gave 55/26 mixture of **2a**/**3a** before catalytic system became inactive due to gold reduction under the reaction conditions to form "gold mirror" (Table 1, Entry 13). Our assumption, that the chloride ion is responsible for decreasing of catalytic activity of the gold(I) complex was confirmed by the experiment where AgOTf was used as additive to precipitate off chloride ion: **3a** was obtained in high yield and only 23% of **2a** left intact (Table 1, Entry 14). Use of silver $AgNTf_2$ instead of AgOTf in 1,2-dichloroethane gave even better result (Table 1, Entries 15, 16). Elimination of chloride ions from the reaction mixture by use of air-stable non hydroscopic bis((trifluoromethyl)sulfonyl)amide iron(II), which has not earlier been reported as a catalyst for isomerization of 5-alkoxyisoxazole to 2*H*-azirine-2-carboxylate, gave the best result (Table 1, Entry 17). The reaction was then performed under the conditions of domino relay catalysis, affording practically the same isolated yield of nicotinate **3a** (Table 1, Entry 18).

Table 1. Optimization of catalytic system.



1a **2a** **3a**

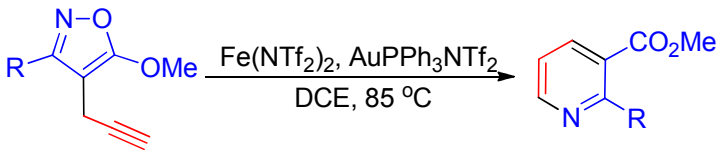
Entry	Catalyst or additive A/B[a]	Solvent	Temperature, T^1/T^2 [°C]	Time, t^1/t^2 [h]	Yield[b] of **2**/**3** [%]
1	-	Dioxane	155	6	0/0
2	$FeCl_2 \cdot 4H_2O$	MeCN	24	2	98/0
3	$FeCl_2 \cdot 4H_2O$	Dioxane	155	6	89/0
4	$Mo(CO)_6$	Dioxane	85	36	95/0
5	CuIPrCl	Dioxane	85	36	75/15
6	DBU[d]	PhCl	130	6	0/0
7	$FeCl_2 \cdot 4H_2O$/DBU[d]	Dioxane	155/155	6/6	0/28
8	$Mo(CO)_6$/DBU[d]	Dioxane	85/155	36/24	0/26
9	IPrCuCl/DBU[d]	Dioxane	85/155	36/24	0/38
10	Ph_3PAuCl+AgOTf	DCE	85	18	-
11	IPrAuCl+AgOTf	DCE	85	18	-
12	$Ph_3PAuNTf_2$	DCE	85	18	-
13	$FeCl_2 \cdot 4H_2O$/$Ph_3PAuNTf_2$	DCE	85/85	1/12	55/26
14	$FeCl_2 \cdot 4H_2O$+AgOTf[e]/$Ph_3PAuNTf_2$	DCE	85/85	1/12	23/75
15	$FeCl_2 \cdot 4H_2O$+$AgNTf_2$[e]/$Ph_3PAuNTf_2$	MeCN	85/85	1/24	68/27
16	$FeCl_2 \cdot 4H_2O$+$AgNTf_2$[e]/$Ph_3PAuNTf_2$	DCE	85/85	1/24	16/82
17	$FeNTf_2$/$Ph_3PAuNTf_2$	DCE	85/85	1/24	5/93 (71[c])
18	$FeNTf_2$+$Ph_3PAuNTf_2$	DCE	85	24	-/72[c]

[a] Catalyst or additive loading was 5 mol% unless otherwise stated.
[b] Yields were determined by ^{1}H NMR spectroscopy with 2-methylnaphthalene as internal standard.
[c] Isolated yield.
[d] 300 mol%.
[e] 10 mol%.

With optimal reaction conditions in hand, we performed isomerizations of isoxazoles **1a-i**, with various substituents in position 3, into nicotinates **3a-i**. 3-Aryl and 3-alkyl substituted 5-methoxy-4-(prop-2-yn-1-yl)isoxazoles **1a-i** upon heating in 1,2-dichloroethane in the presence of $Fe(NTf_2)_2$ and

$Au(PPh_3)NTf_2$ afforded 2-substituted nicotinates in high yields with the exception for 3-cyclopropylisoxazole (Table 2). 3-Bromophenyl-, 4-nitrophenyl, cyclopropyl and *tert*-bytyl substituted isoxazoles needed longer time for the isomerization. Besides, 3-alkyl substituted isoxazoles required higher gold(I) catalyst loading for the reaction to complete.

Table 2. Synthesis of 2-substituted methyl nicotinates from 4-propargylisoxazoles under Fe(II)/Au(I) relay catalysis.[a]



1a-i **3a-i**

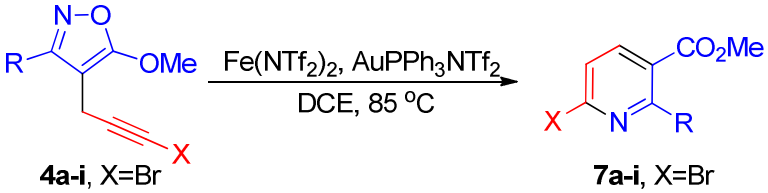
Entry	R	Time, [h]	Yield,[b] [%]
1	**a**, Ph	20	72
2	**b**, 4-MeC_6H_4	20	82
3	**c**, 4-$MeOC_6H_4$	18	94
4	**d**, 4-ClC_6H_4	22	91
5	**e**, 4-BrC_6H_4	24	90
6	**f**, 3-BrC_6H_4	30	67
7	**g**, 4-$NO_2C_6H_4$	32	90
8	**h**, *c*-C_3H_5 [c]	38	61
9	**i**, *t*-C_4H_9 [c]	46	93

[a] A mixture of 0.5 mmol of **1**, 25 μmol (5 mol%) of $Fe(NTf_2)_2$ and 25 μmol (5 mol%) of $Ph_3PAuNTf_2$ in 2 mL of DCE was heated at 85°C in a screw-cap tube.
[b] Yield after column chromatography on silica deactivated by Et_3N.
[c] 50 μmol (10 mol%) of $Ph_3PAuNTf_2$ was used.

Bromine or iodine can be readily introduced to terminal acetylene carbon atom by reaction with *N*-bromo- or *N*-iodosuccinimide in the presence of silver(I).[25] This reaction can be used for the preparation of 4-(3-halopropargyl)isoxazoles from the corresponding 4-propargylisoxazoles, but it is useless for the synthesis of 2-(3-halopropargyl)-2*H*-azirines from the corresponding 2-propargyl-2*H*-azirines due to their instability under the halogenation conditions. Because of this, the discussed transformation of isoxazoles could be potentially a useful method for the preparation of highly

sought 2-halopyridines. 4-(3-Halopropargyl)isoxazoles **4a-i,5a-c,6** were prepared from isoxazoles **3a-i** and *N*-halosuccinimides. To our delight all isoxazoles **4-6** obtained underwent the isomerization under our standard Fe(II)/Au(I) relay catalysis conditions providing 6-halonicotinates in generally good yields that were only a bit lower than for the corresponding non-halogenated nicotinates (Table 3).

Table 3. Synthesis of 2-substituted methyl 6-halonicotinates from 4-(3-haloprop-2-yn-1-yl)isoxazoles under Fe(II)/Au(I) relay catalysis. [a]



4a-i, X=Br
5a-c, X=I
6, X=Cl

7a-i, X=Br
8a-c, X=I
9, X=Cl

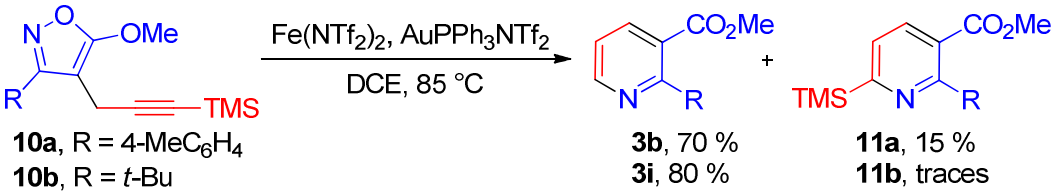
Entry	Isoxazole	R	Time, [h]	Yield,[b] [%]
1	**4a**	Ph	24	**7a**, 70
2	**4b**	4-MeC_6H_4	19	**7b**, 72
3	**4c**	4-$MeOC_6H_4$	30	**7c**, 53
4	**4d**	4-ClC_6H_4	22	**7d**, 80
5	**4e**	4-BrC_6H_4	25	**7e**, 75
6	**4f**	4-$NO_2C_6H_4$	45	**7f**, 80
7	**4g**	Me[c]	48	**7g**, 40
8	**4h**	*c*-C_3H_5[c]	44	**7h**, 45
9	**4i**	*t*-C_4H_9[c]	40	**7i**, 83
10	**5a**	Ph	23	**8a**, 88
11	**5b**	4-$MeOC_6H_4$	23	**8b**, 67
12	**5c**	4-BrC_6H_4	24	**8c**, 71
13	**6**	Ph	21	**9**, 63

[a] A mixture of 1 mMol of **4-6**, 50 μmol (5 mol %) of $Fe(NTf_2)_2$ and 50 μmol (5 mol%) of $Ph_3PAuNTf_2$ in 5 mL of DCE was heated at 85°C in a screw-cap tube.
[b] Yield after column chromatography on silica deactivated by Et_3N.
c 25 μmol (2.5 mol%) of $Ph_3PAuNTf_2$ were added after first 24 hours of the reaction.

3-Alkyl-substituted isoxazoles (**4g-i**) again required longer reaction times and bigger gold(I) catalyst loads for the full conversion. The yields of 2-methyl- and 2-cyclopropyl-substituted methyl 6-bromonicotinates **7g**,**h** are the lowest among of the investigated substrates. We suppose that the

low yields of bromonicotinates **7g**,**h** are caused by the relatively lower stability of the corresponding starting isoxazoles and intermediate azirines.

It is worth mentioning that TMS-group of 4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazoles is lost partly or even completely under the transformation into nicotinates under the Fe(II)/Au(I) relay catalysis conditions. Thus, only 15% of 6-(trimethylsilyl)nicotinate **11a**, together with the main product, nicotinate **3b**, was isolated, when isoxazole **10a** was used as the starting material. Isoxazole **11b** gave only the desilylation product (**3i**) (Scheme 2).



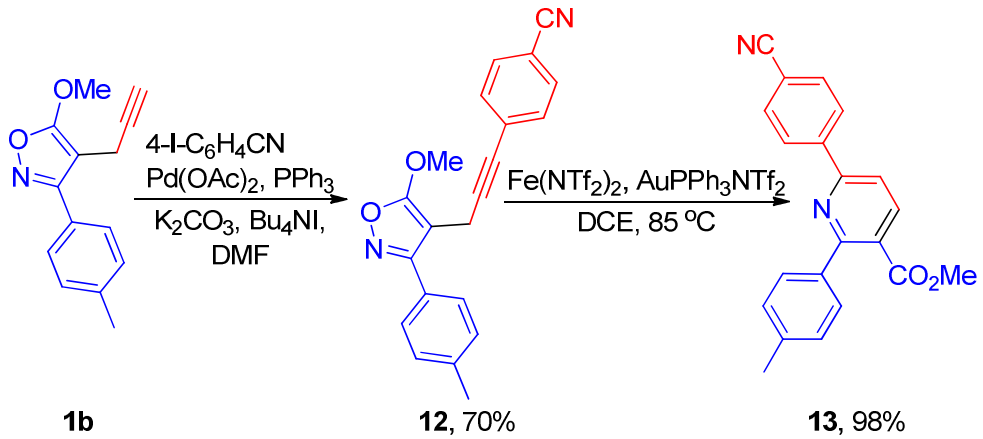
10a, R = 4-MeC_6H_4
10b, R = *t*-Bu

3b, 70 %
3i, 80 %

11a, 15 %
11b, traces

Scheme 2. Isomerization of 4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazoles to nicotinates under Fe(II)/Au(I) relay catalysis.

Electron-deficient aryl groups can be introduced to acetylene moiety of 4-propargylisoxazole by copper-free Sonogashira cross-coupling protocol, e.g. **12**. Diarylnicotinate **13** was prepared in quantitative yield by domino isomerization of propargylisoxazole **12** under the relay catalysis conditions (Scheme 3). Sonogashira reaction of **1b** with electron-rich aryl iodides did not, however, proceed in copper-free conditions, while the standard cross-coupling procedure gave low yields of target products due to side reactions in the presence of copper catalyst.



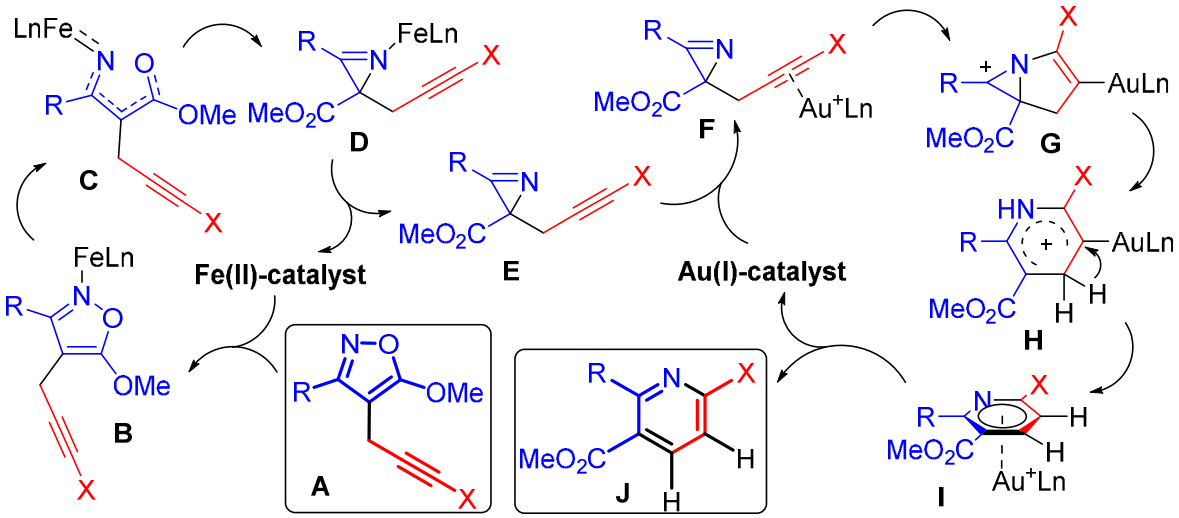
1b

12, 70%

13, 98%

Scheme 3. Synthesis of 2,6-diarylated nicotinate under relay catalysis conditions.

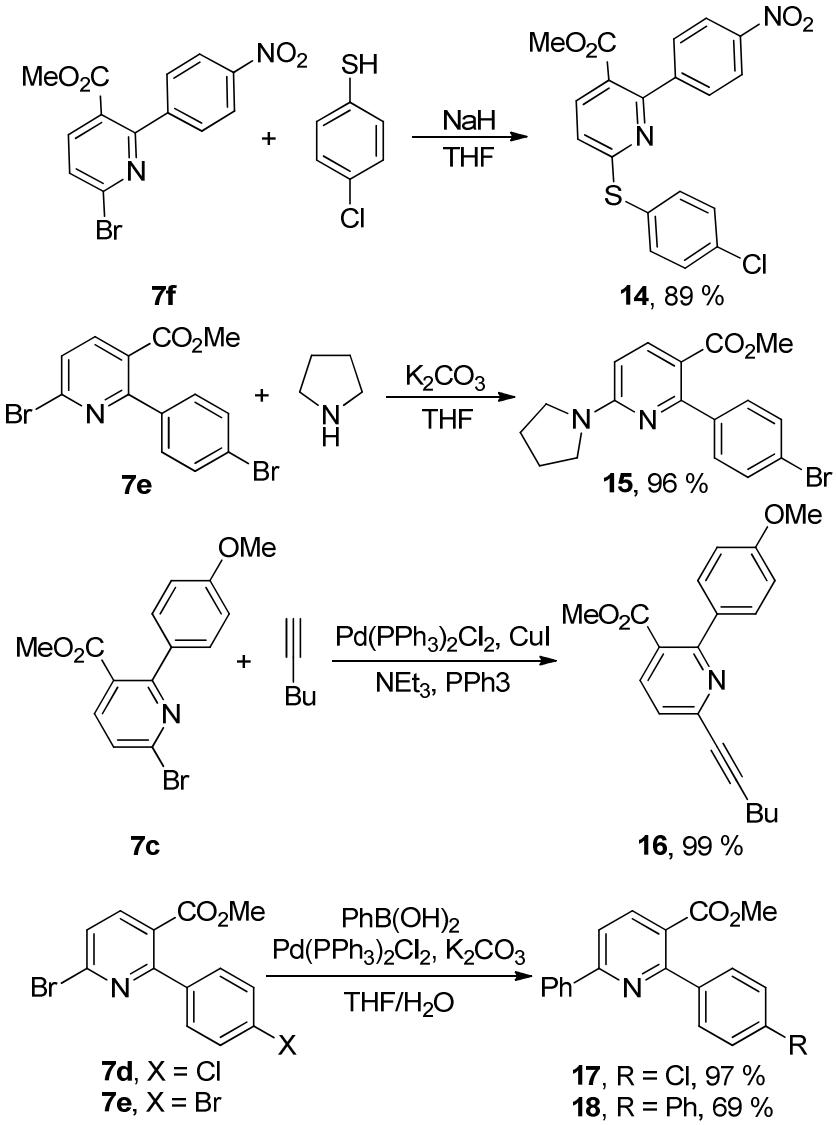
A proposed mechanism for the formation of pyridines **J**, based on literature analysis of the transformations of 5-alkoxyisoxazoles **A** under Fe(II)-catalysis[18-20, 26] and the transformations of 2-propargyl-2*H*-azirines **E** under Au(I)-catalysis,[17, 27] is presented in Scheme 4. It involves the isoxazole ring opening in isoxazole complex **B** with the formation of Fe-nitrene complex **C**, the cyclization of **C** into Fe-azirine complex **D**, formation of Au-acetylene complex **F**, 5-*endo*-dig cyclization by nucleophilic attack into complex **G** followed by the azirine ring expansion in **G** and proton transfer in **H**.



Scheme 4. Proposed mechanism of nicotinate formation under Fe(II)/Au(I) relay catalysis.

Finally, we tried some substitution and cross-coupling reactions of 6-halonicotinates obtained (Scheme 5). Reactions of 6-bromonicotynates **7f** and **7e** with sodium 4-chlorobenzenethiolate and pyrrolidine proceeded smoothly to give products of nucleophilic aromatic substitution **14** and **15** in excellent yields. Sonogashira cross-coupling of **7c** with hex-1-yn provided 6-(alk-1-yn-1-yl)nicotinate **16** in quantitative yield under standard reaction conditions. Suzuki cross-coupling reaction of phenylboronic acid with methyl 6-bromo-2-(4-chlorophenyl)nicotinate **7d** proceeds selectively affording 2,6-diarylnicotinate **17** in nearly quantitative yield. In contrast, methyl 6-

bromo-2-(4-bromophenyl)nicotinate **7e** gives bis-cross-coupling product, azaquaterphenyl **18**, as the result of substitution of both bromines in the starting material. These high yield reactions demonstrate a high synthetic potential of 6-halonicotinates, which are available via the developed method, for the preparation of variously substituted 2,6-disubstituted pyridines.



Scheme 5. Synthesis of 2,6-substituted nicotinates from 6-halonicotinates by SN_{Ar}- and cross-coupling reactions.

CONCLUSION

In conclusion, an efficient synthesis of nicotynates by the domino isomerization of propargylisoxazoles under Fe(II)/Au(I) relay catalysis was developed. Easy modification of propargylisoxazoles into halopropargylisoxazoles provides direct approach to highly sought 6-halonicotinates. Use of bis((trifluoromethyl)sulfonyl)amide iron(II) as an air-stable non hygroscopic catalyst for first step of the tandem isomerization, the transformation of isoxazole into 2*H*-azirine, allows realization of Fe(II)/Au(I) relay catalytic scheme due to that $FeNTf_2$ does not inhibit catalytic activity of gold(I) complexes. A high synthetic potential of 6-halonicotinates, which are available via the developed method, for the preparation of variously substituted 2,6-disubstituted pyridines by substitution and metal-catalyzed cross-coupling reactions was also demonstrated.

EXPERIMENTAL SECTION

General Information and Methods

Melting points were determined on a capillary melting point apparatus using unsealed capillary. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$ with NMR-spectrometer. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane (TMS δ 0.00). ^{1}H NMR spectra were calibrated according to the residual peak of $CHCl_3$ (7.26 ppm). For all new nicotinates and isoxazoles $^{13}C\{^{1}H\}$ and ^{13}C DEPT135 were recorded and calibrated according to the peak of $CDCl_3$ (77.00 ppm). Mass spectra were recorded on a HRMS-ESI-QTOF mass-analyzer, electrospray ionization, positive mode. Thin-layer chromatography (TLC) was conducted on aluminium sheets with 0.2 mm silica gel with fluorescent indicator, silica 60 M was used for column chromatography.

Acetonitrile and 1,2-dichloroethane were distilled successively over phosphorous pentoxide and calcined potassium carbonate under argon atmosphere prior before use. Tetrahydrofuran, 1,4-dioxane and toluene were distilled from sodium benzophenone-ketyl. Triethylamine was

distilled from sodium. Acetone was distilled from calcined potassium carbonate under argon atmosphere. Commercial *N,N*-dimethylformamide of HPLC-grade was used without purification.

Synthesis of Starting Materials

Synthesis of Catalysts and Precursors

Synthesis of 3-substituted-3-oxopropanoates was performed according to the published procedure[28] with exception for commercial ethyl benzoylacetate and ethyl 3-(4-nitrophenyl)-3-oxopropanoate that were used without purification. Bis((trifluoromethyl)sulfonyl)amide [triphenylphosphane]gold(I) was synthesized by V. A. Rassadin procedure.[29] Bis((trifluoromethyl)sulfonyl)amide iron(II) was synthesized by M. P. Sibi procedure.[30]

General procedure I for the synthesis of alkyl 2-aroylpent-4-ynoates 19 (corresponds to slightly modified procedure of B. Kirschleger et al).[31] Alkyl 3-aryl-3-oxopropanoate (10 mmol) and propargylbromide (1.31 g, 11 mmol) were dissolved in dry acetone (10 mL), calcined and mortar-grounded potassium carbonate (2.07 g, 15 mmol) and dry NaI (0.37 g, 2.5 mmol) were then added and the mixture was stirred at room temperature until complete consumption of the starting ester (monitored by TLC). The mixture was diluted with water, extracted with ether, the organic phase was washed with water and brine, dried over sodium sulfate and all volatiles were removed *in vacuo*. The product could be purified by column chromatography or vacuum distillation, but generally it was used in further steps without any purification.

Ethyl 2-benzoylpent-4-ynoate 19a was obtained following the general procedure I from ethyl 3-oxo-3-phenylpropanoate (9.60 g, 50 mmol) in 9.50 g (83%) yield as a colorless oil, bp 130-5 °C (1.0 Torr) (lit. bp 130 °C (0.9 Torr)[32]). Spectral data were in agreement with previously reported values.[33]

Ethyl 2-(4-methoxybenzoyl)pent-4-ynoate 19c was obtained following the general procedure I from ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (5.60 g, 25.0 mmol) in 6.60 g yield as a light-

yellow oil and used without any purification. Spectral data were in agreement with previously reported values.[34]

Ethyl 2-(4-bromobenzoyl)pent-4-ynoate 19e was obtained following the general procedure I from ethyl 3-(4-bromophenyl)-3-oxopropanoate (1.00g, 3.7 mmol), in 1.34 g yield as a light-brown oil and used without any purification. Spectral data were in agreement with previously reported values.[34]

Ethyl 2-(4-nitrobenzoyl)pent-4-ynoate 19g was obtained following the general procedure I from ethyl 3-(4-nitrophenyl)-3-oxopropanoate (3.00 g, 12.6 mmol) in 3.22 g yield as a dark-brown oil and used without any purification. Spectral data were in agreement with previously reported values.[35]

General procedure II for the synthesis of 3-aryl-4-(prop-2-yn-1-yl)isoxazol-5(4H)-ones 20.

Alkyl 2-aroylpent-4-ynoate **19** (10 mmol) was dissolved in ethanol (25 mL) and hydroxylamine hydrochloride was then added (1.75 g, 25 mmol). The mixture was stirred at room temperature for several days until TLC showed absence either of the starting ester or of any further changes. The mixture was concentrated *in vacuo* and the residue was portioned between water and ether, the layers were separated and the aqueous one was extracted with ether. The combined organic phases were washed with water and extracted with 5% aqueous potassium hydroxide solution and the combined basic extracts were washed with small portion of ether prior to acidification with concentrated hydrochloric acid. If the product solidified it was separated by filtration, washed with water and dried in air, otherwise it was extracted with ether. The ether solution was washed with water, brine and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was forced to crystallize by ultrasound sonification from hexanes/ether mixture. The compounds obtained were used in further steps without additional purification, though could be purified by recrystallization.

3-Phenyl-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one 20a was obtained following the general procedure II from ethyl 2-benzoylpent-4-ynoate **19a** (9.41 g, 41 mmol) in 6.02 g (74%) yield as a peach-

colored solid, mp 130.5-131.5 °C (heptane/dichloromethane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (t, *J* = 2.6 Hz, 1H), 2.85 (ddd, *J* = 17.1, 5.3, 2.6 Hz, 1H), 3.01 (ddd, *J* = 17.1, 4.4, 2.6 Hz, 1H), 3.98 (t, *J* = 4.9 Hz, 1H), 7.49-7.58 (m, 3H), 7.66-7.68 (m, 2H). Spectra shows ~16% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (t, *J* = 2.7 Hz, 1H), 3.32 (d, *J* = 2.7 Hz, 2H), 7.49-7.58 (m, 3H), 7.66-7.69 (m, 2H), 8.34 (br. s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1 (CH_2), 44.3 (CH), 72.7 (CH), 76.3 (C), 127.0 (CH), 127.3 (C), 129.3 (CH), 132.0 (CH), 165.0 (C), 176.4 (C) (only major isoxazole-5(4*H*)-one form signals are reported). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_9NNaO_2^+$ 222.0525; Found 222.0530.

3-(4-Methylphenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one 20b. Ethyl 2-(4-methylbenzoyl)pent-4-ynoate **19b** was first obtained following the general procedure I from ethyl 3-(4-methylphenyl)-3-oxopropanoate (8.25 g, 40 mmol) in 7.81 g (80%) yield as a colorless oil with bp 160-2 °C (0.5 Torr) [^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.18 (t, *J* = 7.1 Hz, 3H), 1.98 (t, *J* = 2.6 Hz, 1H), 2.42 (s, 3H), 2.83 (ddd, *J* = 17.0, 7.1, 2.6 Hz, 1H), 2.98 (ddd, *J* = 17.0, 7.7, 2.6 Hz, 1H) 4.16 (qd, *J* = 7.1, 1.7 Hz, 2H), 4.54 (t, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 2H)]. Compound **19b** (5.98g, 24 mmol) was then treated with hydroxylamine hydrochloride in accordance with the general procedure II to provide the title isoxazolone **20b** in 3.50 g (67%) yield as a light-beige solid, mp 109-111 °C (heptane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.04 (t, *J* = 2.6 Hz, 1H), 2.42 (s, 3H), 2.84 (ddd, *J* = 17.1, 5.4, 2.6 Hz, 1H), 2.99 (ddd, *J* = 17.1, 4.4, 2.6 Hz, 1H), 3.94-3.96 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H). Spectra shows ~15% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (t, *J* = 2.6 Hz, 1H), 2.44 (s, 3H), 3.31 (d, *J* = 2.6 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 8.28 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.2 (CH_2), 21.6 (CH_3), 44.3 (CH), 72.7 (CH), 76.3 (C), 124.3 (C), 126.8 (CH), 130.0 (CH), 142.7 (C), 164.9 (C), 176.6 (C) (only major isoxazole-5(4*H*)-one form signals are reported). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{11}NNaO_2^+$ 236.0682; Found 236.0684.

3-(4-Methoxyphenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one 20c was obtained following the general procedure II from ethyl 2-(4-methoxybenzoyl)pent-4-ynoate **19c** (2.95 g, 11 mmol) in 1.92 g (73%) yield as a light rose-colored solid, mp 126-127 °C (water). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (t, *J* = 2.6 Hz, 1H), 2.84 (ddd, *J* = 17.1, 5.4, 2.6 Hz, 1H), 2.99 (ddd, *J* = 17.1, 4.5, 2.6 Hz, 1H), 3.87 (s, 3H), 3.93 (t, *J* = 4.9 Hz, 1H), 6.98-7.02 (m, 2H), 7.60-7.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.3 (CH_2), 44.3 (CH), 55.5 (CH_3), 72.6 (CH), 76.4 (C), 114.8 (CH), 119.4 (C), 128.6 (CH), 162.5 (C), 164.5 (C), 176.7 (C). Spectra shows ~14% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (t, *J* = 2.7 Hz, 1H), 3.31 (d, *J* = 2.7 Hz, 2H), 3.88 (s, 3H), 7.04-7.06 (m, 2H), 7.63-7.66 (m, 2H), 8.14 (br. s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.6 (CH_2), 55.5 (CH_3), 69.3 (CH), 80.3 (C), 97.8 (C), 114.8 (CH), 119.0 (C), 129.3 (CH), 162.3 (C), 162.6 (C), 172.6 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{12}NO_3^+$ 230.0812; Found 230.0817.

3-(4-Chlorophenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one 20d. Ethyl 2-(4-chlorobenzoyl)pent-4-ynoate **19d** was first obtained following the general procedure I from ethyl 3-(4-chlorophenyl)-3-oxopropanoate (4.53 g, 20.0 mmol) in 5.33 g yield as a light-brown oil. [^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (t, *J* = 7.1 Hz, 3H), 1.98 (t, *J* = 2.7 Hz, 1H), 2.85 (ddd, *J* = 17.0, 7.4, 2.7 Hz, 1H), 2.92 (ddd, *J* = 17.0, 7.4, 2.7 Hz, 1H), 4.16 (qd, *J* = 7.1, 1.3 Hz, 2H), 4.51 (t, *J* = 7.4 Hz, 1H), 7.43-7.48(m, 2H), 7.96-7.99 (m, 2H) (spectra shows ~ 5% of enol form and ~ 15% of dipropargylated product δ 1.16 (t, *J* = 7.3 Hz, 3H), 2.02 (t, *J* = 2.7 Hz, 2H), 3.12 (qd, *J* = 17.4, 2.7 Hz, 4H), 4.19-4.25 (m, 2H), 7.40-7.42 (m, 2H), 7.77-7.79 (m, 2H)]. The entire crude compound **19d** obtained was used in further steps without any purification. It was treated with hydroxylamine hydrochloride in accordance with the general procedure II to provide the title isoxazolone **20d** in 3.14 g yield (67% yield on two steps based on the starting ethyl 3-(4-chlorophenyl)-3-oxopropanoate) as a sand-colored solid, mp 134-135 °C (light petroleum/dichloromethane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (t, *J* = 2.7 Hz, 1H), 2.84 (ddd, *J* = 17.2, 5.3, 2.7 Hz, 1H), 3.00 (ddd, *J* = 17.2, 4.5, 2.7 Hz, 1H), 3.95 (t, *J* = 4.9 Hz, 1H), 7.48-7.50 (m, 2H), 7.61-7.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1

(CH_2), 44.1 (CH), 72.9 (CH), 76.1 (C), 125.6 (C), 128.2 (CH), 129.7 (CH), 138.4 (C), 164.1 (C), 176.2 (C). Spectra shows ~15% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (t, *J* = 2.6 Hz, 1H), 3.30 (d, *J* = 2.7 Hz, 2H), 7.52-7.54 (m, 2H), 7.63-7.65 (m, 2H), 8.44 (br. s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.5 (CH_2), 69.7 (CH), 79.8 (C), 99.0 (C), 125.1 (C), 129.1 (CH), 129.8 (CH), 138.2 (C), 161.5 (C), 172.3 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_8{}^{35}ClNNaO_2^+$ 258.0136; Found 258.0141.

3-(4-Bromophenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one 20e was obtained following the general procedure II from crude ethyl 2-(4-bromobenzoyl)pent-4-ynoate **19e** (2.88 g) in 1.84 g yield as a yellowish solid, mp 137-138 °C (water). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (t, *J* = 2.7 Hz, 1H), 2.84 (ddd, *J* = 17.2, 5.2, 2.7 Hz, 1H), 3.00 (ddd, *J* = 17.2, 4.3, 2.7 Hz, 1H), 3.95 (t, *J* = 4.9 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1 (CH_2), 44.0 (CH), 73.0 (CH), 76.1 (C), 126.1 (C), 126.8 (C), 128.3 (CH), 132.7 (CH), 164.2 (C), 176.1 (C). Spectra shows ~14% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (t, *J* = 2.5 Hz, 1H), 3.30 (d, *J* = 2.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 8.43 (br. s, 1H). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_9BrNO_2^+$ 277.9811; Found 277.9803.

3-(3-Bromophenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one 20f. Ethyl 2-(3-bromobenzoyl)pent-4-ynoate **19f** was first obtained following the general procedure I from ethyl 3-(3-bromophenyl)-3-oxopropanoate (2.00 g, 7.4 mmol) in 2.23 yield as a light-brown oil. [^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (t, *J* = 7.2 Hz, 3H), 1.99 (t, *J* = 2.6 Hz, 1H), 2.86 (ddd, *J* = 17.0, 7.4, 2.6 Hz, 1H), 2.92 (ddd, *J* = 17.0, 7.2, 2.6 Hz, 1H), 4.17 (qd, *J* = 7.2, 3.4 Hz, 2H), 4.50 (t, *J* = 7.4 Hz, 1H), 7.38 (td, *J* = 7.9, 0.8 Hz, 1H), 7.73 (ddd, *J* = 7.9, 1.8, 0.8 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 8.17 (t, *J* = 1.8 Hz, 1H) (spectra shows ~ 13% of enol form and ~14% of dipropargylated product δ 1.17 (t, *J* = 7.1 Hz, 3H), 2.03 (t, *J* = 2.7 Hz, 2H), 3.12 (qd, *J* = 17.3, 2.7 Hz, 4H), 4.18-4.24 (m, 2H), 7.47-7.54 (m, 1H), 7.59-7.63 (m, 1H), 8.02-8.04 (m, 1H)]. It was used in further steps without any purification. The entire compound **19f** obtained was treated with hydroxylamine hydrochloride in accordance with the

general procedure II to provide the title isoxazolone **20f** in 0.732 g yield (36% yield on two steps based on the starting ethyl 3-(3-bromophenyl)-3-oxopropanoate) as a yellowish solid, mp 126-128 °C (water). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.08 (m, 1H), 2.84-2.88 (m, 1H), 2.98-3.02 (m, 1H), 3.93 (t, *J* = 4.8 Hz, 1H), 7.27-7.41 (m, 1H), 7.59-7.63 (m, 1H), 7.68-7.70 (m, 1H), 7.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.0 (CH_2), 44.0 (CH), 73.0 (CH), 76.1 (C), 123.4 (C), 125.5 (CH), 129.0 (C), 129.8 (CH), 130.8 (CH), 135.0 (CH), 163.9 (C), 176.0 (C). Spectra shows ~13% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (M, 1H), 3.32 (m, 2H), 8.11 (br. s, 1H) (only well-resolved characteristic signals are given). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_9BrNO_2^+$ 277.9811; Found 277.9809.

3-(4-Nitrophenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one 20g was obtained following the general procedure II from crude ethyl 2-(4-nitrobenzoyl)pent-4-ynoate **19g** (3.10 g) in 1.91 g yield as a brick-colored solid, mp 123-127 °C (water). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.07 (t, *J* = 2.7 Hz, 1H), 2.88 (ddd, *J* = 17.3, 5.3, 2.7 Hz, 1H), 3.04 (ddd, *J* = 17.3, 4.6, 2.7 Hz, 1H), 4.01 (t, *J* = 4.9 Hz, 1H), 7.88-7.90 (m, 2H), 8.36-8.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.0 (CH_2), 44.0 (CH), 73.3 (CH), 75.9 (C), 124.5 (CH), 128.0 (CH), 133.0 (C), 149.8 (C), 163.5 (C), 175.6 (C). Spectra shows ~9% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.08 (t, *J* = 2.7 Hz, 1H), 3.35 (d, *J* = 2.7 Hz, 2H), 7.89-7.92 (m, 2H), 8.40-8.42 (m, 2H). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_9N_2O_4^+$ 245.0557; Found 245.0553.

Synthesis of Isoxazoles

General procedure III for the synthesis of 3-substituted 5-methoxy-4-(prop-2-yn-1-yl)isoxazoles 1, 10.

3-Substituted 4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one **20** (or **22**) was worked up with excess of ethereal diazomethane solution and 3-substituted 5-methoxy-4-(prop-2-yn-1-yl)isoxazole **1** (or 5-methoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10b-d**) were isolated by chromatography according to the previously reported procedure.[19a]

5-Methoxy-3-phenyl-4-(prop-2-yn-1-yl)isoxazole 1a was obtained following the general procedure III from 3-phenyl-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one (1.08 g, 5.4 mmol) **20a** in 0.86 g (74%) yield as a sand-colored solid, mp 56-58 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.04 (t, *J* = 2.7 Hz, 1H), 3.26 (d, *J* = 2.7 Hz, 2H), 4.17 (s, 3H), 7.46-7.49 (m, 3H), 7.72-7.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.5 (CH_2), 58.0 (CH_3), 68.9 (CH), 81.2 (C), 86.9 (C), 128.0 (CH), 128.8 (CH), 129.5 (C), 129.8 (CH), 164.3 (C), 169.6 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{11}NNaO_2^+$ 236.0682; Found 236.0680.

5-Methoxy-3-(4-methylphenyl)-4-(prop-2-yn-1-yl)isoxazole 1b was obtained following the general procedure III from 3-(4-methylphenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one **20b** (1.52 g, 7.1 mmol) in 1.09 g (67%) yield as an yellow solid, mp 70.5-72.0°C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.04 (t, *J* = 2.7 Hz, 1H), 2.41 (s, 3H), 3.25 (d, *J* = 2.7 Hz, 2H), 4.16 (s, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.6 (CH_2), 21.4 (CH_3), 57.9 (CH_3), 68.8 (CH), 81.3 (C), 86.8 (C), 126.6 (C), 127.8 (CH), 129.5 (CH), 139.8 (C), 164.2 (C), 169.5 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}NO_2^+$ 228.1019; Found 228.1026.

5-Methoxy-3-(4-methoxyphenyl)-4-(prop-2-yn-1-yl)isoxazole 1c was obtained following the general procedure III from 3-(4-methoxyphenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one **20c** (1.00 g, 4.40 mmol) in 0.83 g (77%) yield as a colorless solid, mp 73-74 °C (light petroleum/ethyl acetate). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.04 (t, *J* = 2.7 Hz, 1H), 3.25 (d, *J* = 2.7 Hz, 2H), 3.85 (s, 3H), 4.15 (s, 3H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.6 (CH_2), 55.3 (CH_3), 57.9 (CH_3), 68.8 (CH), 81.4 (C), 86.7 (C), 114.2 (CH), 121.9 (C), 129.3 (CH), 160.8 (C), 163.9 (C), 169.5 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}NO_3^+$ 244.0968; Found 244.0969.

3-(4-Chlorophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole 1d was obtained following the general procedure III (with exception that the product was purified by recrystallization from

methanol instead of column chromatography) from 3-(4-chlorophenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one **20d** (3.00 g, 12.8 mmol) in 2.10 g (66%) yield as an yellow solid, mp 107-108 °C (methanol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.04 (t, *J* = 2.7 Hz, 1H), 3.24 (d, *J* = 2.7 Hz, 2H), 4.17 (s, 3H), 7.44-7.47 (m, 2H), 7.67-7.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.5 (CH_2), 58.1 (CH_3), 69.1 (CH), 81.0 (C), 86.9 (C), 127.9 (C), 129.1 (CH), 129.3 (CH), 136.0 (C), 163.3 (C), 169.7 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}ClNO_2^+$ 248.0473; Found 248.0477.

3-(4-Bromophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole 1e was obtained following the general procedure III from 3-(4-bromophenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one **20e** (1.00 g, 3.60 mmol) in 0.88 g (84%) yield as a colorless solid, mp 107-108 °C (light petroleum/ethyl acetate). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.04 (t, *J* = 2.7 Hz, 1H), 3.24 (d, *J* = 2.7 Hz, 2H), 4.17 (s, 3H), 7.62 (*pseudo*-s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.5 (CH_2), 58.1 (CH_3), 69.2 (CH), 81.0 (C), 86.8 (C), 124.3 (C), 128.4 (C), 129.5 (CH), 132.0 (CH), 163.3 (C), 169.7 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}BrNO_2^+$ 291.9968; Found 291.9967.

3-(3-Bromophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole 1f was obtained following the general procedure III from 3-(3-bromophenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one **20f** (0.63 g, 2.27 mmol) in 0.46 g (69%) yield as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (t, *J* = 2.7 Hz, 1H), 3.25 (d, *J* = 2.7 Hz, 2H), 4.17 (s, 3H), 7.33-7.37 (m, 1H), 7.59-7.61 (m, 1H), 7.67-7.69 (m, 1H), 7.92 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.5 (CH_2), 58.1 (CH_3), 69.2 (CH), 80.9 (C), 87.0 (C), 122.8 (C), 126.6 (CH), 130.3 (CH), 131.0 (CH), 131.4 (C), 132.8 (CH), 163.1 (C), 169.8 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}BrNO_2^+$ 291.9968; Found 291.9962.

5-Methoxy-3-(4-nitrophenyl)-4-(prop-2-yn-1-yl)isoxazole 1g was obtained following the general procedure III from 3-(4-nitrophenyl)-4-(prop-2-yn-1-yl)isoxazol-5(4*H*)-one **20g** (1.00 g, 4.00 mmol) in 0.72 g (69%) yield as an yellow solid, mp 115-116 °C (light petroleum/ethyl acetate). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.05 (t, *J* = 2.7 Hz, 1H), 3.28 (d, *J* = 2.7 Hz, 2H), 4.20 (s, 3H), 7.96 (d, *J* = 8.8 Hz, 2H), 8.34 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.5 (CH_2), 58.3 (CH_3), 69.6

(CH), 80.6 (C), 87.2 (C), 124.0 (CH), 129.0 (CH), 135.8 (C), 148.6 (C), 162.4 (C), 170.1 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2O_4^+$ 259.0713; Found 259.0710.

3-Cyclopropyl-5-methoxy-4-(prop-2-yn-1-yl)isoxazole 1h. To a solution of 3-cyclopropylisoxazol-5(4*H*)-one[36] (626 mg, 5 mmol) in dry toluene (5 mL) ethylenediamine diacetate[37] (45 mg, 0.25 mmol) was added under argon atmosphere upon cooling with ice bath followed by addition of 3-(trimethylsilyl)propiolaldehyde[38] (1.26 g, 10 mmol) solution in toluene (5 mL). The mixture was stirred with 4 Å molecular sieves for 2 hours at 0 °C under argon and then was subjected to flash chromatography on silica eluting with dichloromethane. The solvents were removed under vacuum at external heater temperature below 30 °C to provide 3-cyclopropyl-4-(3-(trimethylsilyl)prop-2-yn-1-ylidene)isoxazol-5(4*H*)-one **21b** in 712 mg (61%) yield as a brown oil. Because of instability of the substance, NMR spectra of appropriate quality were not recorded. The substance should be used in further steps as soon as possible due to the low stability even when stored below -18 °C under inert atmosphere. The solution of 3-cyclopropyl-4-(3-(trimethylsilyl)prop-2-yn-1-ylidene)isoxazol-5(4*H*)-one **21b** (562 mg, 2.41 mmol) in 15 mL of 1,4-dioxane was added dropwise to the suspension of sodium borohydride (365 mg, 9.65 mmol) in aqueous dioxane (1.5 mL of water and 3.0 mL of 1,4-dioxane) under ice cooling and vigorous stirring. Stirring was continued for 10 min. at 0 °C and for additional 30 min. at room temperature. Water (10 mL) was added and the mixture was carefully acidified with concentrated hydrochloric acid. The product was extracted three times with benzene and combined organic layers were washed with water and brine prior to drying over sodium sulfate. The volatiles were removed *in vacuo* to provide 3-cyclopropyl-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazol-5(4*H*)-one **22b** in 539 mg (95%) yield as a brown viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.13 (s, 9H), 0.91-1.21 (m, 4H), 1.64 (tt, J = 8.2, 5.1 Hz, 1H), 2.82 (dd, J = 17.3, 6.0 Hz, 1H), 2.88 (dd, J = 17.3, 5.0 Hz, 1H), 3.50 (dd, J = 6.0, 5.0 Hz, 1H). Spectra shows ~11% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.13 (s, 9H), 0.91-1.21 (m, 4H), 1.62-1.66 (m, 1H), 3.27 (s, 2H), 7.37 (s, 1H). The compound was

used without further purification. 3-Cyclopropyl-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazol-5(4*H*)-one **22b** (530 mg, 2.25 mmol) was treated with ethereal diazomethane solution in accordance with the general procedure III to provide 3-cyclopropyl-5-methoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10d** in 303 mg (54%) yield as a dark-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.14 (s, 9H), 0.90-1.01 (m, 4H), 1.85 (tt, *J* = 8.3, 5.2 Hz, 1H), 3.24 (s, 2H), 4.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 0.1 (CH_3), 6.6 (CH), 6.7 (CH_2), 12.2 (CH_2), 57.7 (CH_3), 84.8 (C), 87.8 (C), 103.1 (C), 167.1 (C), 168.4 (C). The compound was used without further purification. 3-Cyclopropyl-5-methoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10d** (128 mg, 0.51 mmol) was stirred with 5 mL of saturated potassium carbonate solution in methanol upon cooling with ice bath for four hours. Concentrated hydrochloric acid (2 mL) was added dropwise followed with water (10 mL) and the resulting mixture was extracted 3 times with ether. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine and dried over anhydrous sodium sulfate. The volatiles were removed *in vacuo* and the residue was subjected to flash chromatography on silica eluting with light petroleum/ethyl acetate mixture (10/1) to provide the title compound **1h** (72 mg, 79%) as a pale-yellow oil. The substance darkens upon storage even in a freezer. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91-0.99 (m, 4H), 1.82 (tt, *J* = 8.1, 5.3 Hz, 1H), 2.00 (t, *J* = 2.7 Hz, 1H), 3.20 (d, *J* = 2.7 Hz, 2H), 4.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.5 (CH_3), 6.7 (CH_2), 10.7 (CH_2), 57.7 (CH_3), 68.4 (CH), 80.9 (C), 87.5 (C), 166.9 (C), 168.5 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{12}NO_2^+$ 178.0863; Found 178.0857.

3-(*tert*-Butyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole 1i. 3-(*tert*-Butyl)-4-(3-(trimethylsilyl)prop-2-yn-1-ylidene)isoxazol-5(4*H*)-one **21c** was obtained from 3-(*tert*-butyl)isoxazol-5(4*H*)-one[39] (426 mg, 3.02 mmol) analogously to 3-cyclopropyl-4-(3-(trimethylsilyl)prop-2-yn-1-ylidene)isoxazol-5(4*H*)-one **21b** in quantitative yield (755 mg) as an yellow oil. Spectra shows two (E/Z)-isomers in ~ 1:0.65 ratio. Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.28 (s, 9H), 1.45 (s, 9H), 6.89 (s, 1H). Minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.30 (s, 9H), 1.36 (s, 9H), 6.91 (s,

1H). The compound was used without further purification (in the procedure analogous for compound **22b**) to provide 3-(*tert*-butyl)-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazol-5(4*H*)-one **22c** in quantitative yield (750 mg) as a light-brown oil that solidified upon standing, mp 55-58 °C (benzene). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.13 (s, 9H), 1.33 (s, 9H), 2.91 (d, *J* = 4.8 Hz, 2H), 3.48 (t, *J* = 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ -0.3 (CH_3), 20.8 (CH_2), 28.1 (CH_3), 35.3 (C), 45.6 (CH), 90.2 (C), 99.2 (C), 173.7 (C), 177.4 (C). The compound **22c** (740 mg, 2.97 mmol) was used without further purification to give after work up in accordance with the general procedure III 3-(*tert*-butyl)-5-methoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10b** in 552 mg (70%) yield as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.12 (s, 9H), 1.38 (s, 9H), 3.27 (s, 2H), 4.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 0.1 (CH_3), 13.5 (CH_2), 28.6 (CH_3), 33.6 (C), 57.7 (CH_3), 85.0 (C), 86.6 (C), 104.2 (C), 169.5 (C), 171.6 (C). The compound **10b** (200 mg, 0.75 mmol) without further purification was treated with methanol potassium carbonate solution analogously to 3-cyclopropyl-5-methoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10d** to provide the title compound **1i** in 96 mg (66%) yield as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.38 (s, 9H), 2.00 (t, *J* = 2.7 Hz, 1H), 3.25 (d, *J* = 2.7 Hz, 2H), 4.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.1 (CH_2), 28.6 (CH_3), 33.6 (C), 57.7 (CH_3), 68.5 (CH), 81.7 (C), 86.2 (C), 169.7 (C), 171.4 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{16}NO_2^+$ 194.1176; Found 194.1185.

General procedure IVA for the synthesis of 3-substituted 4-(3-bromoprop-2-yn-1-yl)-5-methoxyisoxazoles 4. 3-Substituted 5-methoxy-4-(prop-2-yn-1-yl)isoxazoles **1** were brominated with *N*-bromosuccinimide in acetone in presence of 25~30 mol% of silver nitrate according to the published procedure.[40]

General procedure IVB for the synthesis of 3-substituted 4-(3-iodoprop-2-yn-1-yl)-5-methoxyisoxazoles 5. 3-Substituted 5-methoxy-4-(prop-2-yn-1-yl)isoxazoles **1** were iodinated with *N*-iodosuccinimide in dry DMF in presence of 25~30 mol% of silver nitrate according to the published procedure[41] with the exception of procedure of product isolation. After the completion the

reaction the mixture was poured into the mixture of saturated aqueous sodium thiosulfate (25 mL) and aqueous ammonia (10 mL) and stirred for an hour in the dark. The precipitate deposited was filtered off washed thoroughly with saturated sodium bicarbonate solution and water, dissolved in ether and worked up with activated charcoal and anhydrous sodium sulfate. Then solids were filtered off, all volatiles were removed *in vacuo* and the residue was vacuum dried to provide the title compound.

General procedure IVC for the synthesis of 3-substituted 4-(3-bromoprop-2-yn-1-yl)-5-methoxyisoxazoles 4. Exchange of trimethylsilyl-group with bromine in 3-substituted 5-methoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazoles **10** was performed with *N*-bromosuccinimide in acetone in presence of 10 mol% of silver nitrate according to the published procedure.[42]

4-(3-Bromoprop-2-yn-1-yl)-5-methoxy-3-phenylisoxazole 4a was obtained following the general procedure IVA from 5-methoxy-3-phenyl-4-(prop-2-yn-1-yl)isoxazole **1a** (213 mg, 1.00 mmol) in 253 mg (87%) yield as a brown viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.27 (s, 2H), 4.17 (s, 3H), 7.46-7.50 (m, 3H), 7.68-7.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.8 (CH_2), 39.5 (C), 58.0 (CH_3), 76.9 (C), 86.5 (C), 128.0 (CH), 128.8 (CH), 129.4 (C), 129.8 (CH), 164.3 (C), 169.4 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}BrNO_2^+$ 291.9968; Found 291.9969.

4-(3-Bromoprop-2-yn-1-yl)-5-methoxy-3-(4-methylphenyl)isoxazole 4b was obtained following the general procedure IVA from 5-methoxy-3-(4-methylphenyl)-4-(prop-2-yn-1-yl)isoxazole **1b** (114 mg, 0.50 mmol) in 136 mg (89%) yield as a brown viscous oil, that crystallized in a freezer to an yellowish solid with mp 57-8 °C (light petroleum). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 3.26 (s, 2H), 4.16 (s, 3H), 7.29 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.8 (CH_2), 21.4 (CH_3), 39.4 (C), 58.0 (CH_3), 77.1 (C), 86.4 (C), 126.5 (C), 127.8 (CH), 129.5 (CH), 139.9 (C), 164.3 (C), 169.6 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{12}BrNNaO_2^+$ 327.9944; Found 327.9947.

4-(3-Bromoprop-2-yn-1-yl)-5-methoxy-3-(4-methoxyphenyl)isoxazole 4c was obtained following the general procedure IVA from 5-methoxy-3-(4-methoxyphenyl)-4-(prop-2-yn-1-yl)isoxazole **1c** (300 mg, 1.23 mmol) in 283 mg (71%) yield as a light-brown solid, mp 71-72 °C (water). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.26 (s, 2H), 3.86 (s, 3H), 4.15 (s, 3H), 6.99-7.02 (m, 2H), 7.63-7.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.9 (CH_2), 39.4 (C), 55.3 (CH_3), 57.9 (CH_3), 77.1 (C), 86.3 (C), 114.3 (CH), 121.8 (C), 129.3 (CH), 160.8 (C), 163.9 (C), 169.5 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}BrNO_3^+$ 322.0073; Found 322.0066.

4-(3-Bromoprop-2-yn-1-yl)-3-(4-chlorophenyl)-5-methoxyisoxazole 4d was obtained following the general procedure IVA from 3-(4-chlorophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole **1d** (743 mg, 3.00 mmol) in 850 mg (87%) yield as a light-yellow solid, mp 83-85 °C (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.25 (s, 2H), 4.17 (s, 3H), 7.45-7.48 (m, 2H), 7.63-7.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (CH_2), 39.9 (C), 58.1 (CH_3), 76.8 (C), 86.5 (C), 127.8 (C), 129.1 (CH), 129.3 (CH), 136.0 (C), 163.3 (C), 169.7 (C). HRMS (ESI-TOF) m/z: $[M + Ag]^+$ Calcd for $C_{13}H_9AgBrClNO_2^+$ 431.8551; Found 431.8558.

3-(4-Bromophenyl)-4-(3-bromoprop-2-yn-1-yl)-5-methoxyisoxazole 4e was obtained following the general procedure IVA from 3-(4-bromophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole **1e** (300 mg, 1.03 mmol) in 300 mg (79%) yield as a yellowish solid, mp 88-89 °C (water). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.25 (s, 2H), 4.17 (s, 3H), 7.57-7.59 (m, 2H), 7.62-7.64 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (CH_2), 39.9 (C), 58.1 (CH_3), 76.8 (C), 86.4 (C), 124.3 (C), 128.3 (C), 129.5 (CH), 132.1 (CH), 163.3 (C), 169.7 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{10}Br_2NO_2^+$ 369.9073; Found 369.9066.

4-(3-Bromoprop-2-yn-1-yl)-5-methoxy-3-(4-nitrophenyl)isoxazole 4f was obtained following the general procedure IVA from 5-methoxy-3-(4-nitrophenyl)-4-(prop-2-yn-1-yl)isoxazole **1g** (300 mg, 1.17 mmol) in 325 mg (83%) yield as an yellowish solid, mp 125-127 °C (water). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.30 (s, 2H), 4.20 (s, 3H), 7.91 (d, J = 8.5 Hz, 2H), 8.35 (d, J = 8.5 Hz, 2H). ^{13}C NMR

($CDCl_3$, 100 MHz): δ 12.7 (CH_2), 40.5 (C), 58.3 (CH_3), 76.4 (C), 86.8 (C), 124.0 (CH), 128.9 (CH), 135.7 (C), 148.6 (C), 162.4 (C), 170.1 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_9BrN_2NaO_4^+$ 358.9638; Found 358.9654.

4-(3-Bromoprop-2-yn-1-yl)-5-methoxy-3-methylisoxazole 4g. 3-Methyl-4-(3-(trimethylsilyl)prop-2-yn-1-ylidene)isoxazol-5(4*H*)-one **21a** was obtained from 3-methylisoxazol-5(4*H*)-one[43] (500 mg, 5.00 mmol) as a brown liquid that solidified in a freezer in a 500 mg (48%) yield by the procedure used for the preparation of isoxazole **21b**. Spectra shows (E/Z)-isomers mixture in ~ 1:0.25 ratio. Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.28 (s, 9H), 2.43 (s, 3H), 6.84 (s, 1H). Minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.30 (s, 9H), 2.21 (s, 3H), 6.60 (s, 1H). The substance was used in further steps without purification due to the low stability even when stored below -18 °C under inert atmosphere. It was reduced into 3-methyl-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazol-5(4*H*)-one **22a** in quantitative yield (505 mg) by the procedure used for the preparation of isoxazole **22b.** Yellow oil that solidified upon standing, mp 68-70 °C (benzene). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.14 (s, 9H), 2.19 (d, J = 0.8 Hz, 3H), 2.75 (dd, J = 17.4, 6.8 Hz, 1H), 2.83 (dd, J = 17.4, 5.0 Hz, 1H), 3.40 (ddd, J = 6.7, 5.0, 0.8 Hz, 1H). Spectra shows ~16% of 5-hydroxyisoxazol form. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.15 (s, 9H), 2.30 (s, 3H), 3.23 (s, 2H), 7.36 (s, 1H). The compound was used without further purification. 5-Methoxy-3-methyl-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10c** was obtained following the general procedure III from isoxazole **22a** (430 mg, 2.00 mmol) in 177 mg (39%) yield as a dark-yellow oil that solidified upon cooling in refrigerator at yellow solid, mp 22-25 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.14 (s, 9H), 2.24 (s, 3H), 3.17 (s, 2H), 4.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 0.1 (CH_3), 11.2 (CH_3), 12.3 (CH_2), 57.7 (CH_3), 85.1 (C), 87.1 (C), 102.6 (C), 162.6 (C), 168.3 (C). The compound **10c** (165 mg, 0.74 mmol) was used without further purification to provide following the general procedure IVC the title compound in 139 mg (82%) yield as a sand-colored solid, mp 51-2 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.23 (s, 3H), 3.15 (s, 2H), 4.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.0 (CH_3), 12.0

(CH_2), 39.0 (C), 57.8 (CH_3), 76.3 (C), 86.5 (C), 162.3 (C), 168.5 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_9BrNO_2^+$ 229,9811; Found 229,9819.

4-(3-Bromoprop-2-yn-1-yl)-3-cyclopropyl-5-methoxyisoxazole 4h was obtained following the general procedure IVC from 3-cyclopropyl-5-methoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10d** (250 mg, 1.00 mmol) in 227 mg (88%) yield as a pale-yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.93-0.98 (m, 4H), 1.78 (tt, J = 8.2, 5.4 Hz, 1H), 3.22 (s, 2H), 4.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 6.5 (CH_3), 6.6 (CH_2), 12.0 (CH_2), 38.9 (C), 57.7 (CH_3), 76.7 (C), 87.1 (C), 166.9 (C), 168.5 (C). HRMS (ESI-TOF) m/z: $[M + Ag]^+$ Calcd for $C_{10}H_{10}AgBrNO_2^+$ 361,8940; Found 361,8930.

4-(3-Bromoprop-2-yn-1-yl)-3-(*tert*-butyl)-5-methoxyisoxazole 4i was obtained following the general procedure IVC from 3-(*tert*-butyl)-5-methoxy-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10b** (130 mg, 0.49 mmol) in 94 mg (71%) yield as a pale-yellow solid mp 68-70 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37 (s, 9H), 3.26 (s, 2H), 4.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.4 (CH_2), 28.6 (CH_3), 33.6 (C), 39.1 (C), 57.7 (CH_3), 77.5 (C), 85.8 (C), 169.6 (C), 171.4 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{15}BrNO_2^+$ 272,0281; Found 272,0279.

4-(3-Iodoprop-2-yn-1-yl)-5-methoxy-3-phenylisoxazole 5a was obtained following the general procedure IVB from 5-methoxy-3-phenyl-4-(prop-2-yn-1-yl)isoxazole **1a** (106 mg, 0.50 mmol) in 120 mg (71%) as off-white solid, mp 102-103.5 °C (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.41 (s, 2H), 4.16 (s, 3H), 7.47-7.51 (m, 3H), 7.68-7.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ -4.7 (C), 13.9 (CH_2), 58.0 (CH_3), 86.7 (C), 91.0 (C), 128.0 (CH), 128.8 (CH), 129.4 (C), 129.8 (CH), 164.3 (C), 169.6 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{10}INNaO_2^+$ 361.9648; Found 361.9657.

4-(3-Iodoprop-2-yn-1-yl)-5-methoxy-3-(4-methoxyphenyl)isoxazole 5b was obtained following the general procedure IVB from 5-methoxy-3-(4-methoxyphenyl)-4-(prop-2-yn-1-yl)isoxazole **1c** (100 mg, 0.40 mmol) in 80 mg (54%) yield as a light-brown solid, mp 109-112 °C (ethyl acetate).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.40 (s, 2H), 3.86 (s, 3H), 4.15 (s, 3H), 6.99-7.01 (m, 2H), 7.64-7.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ -4.8 (C), 14.0 (CH_2), 55.3 (CH_3), 58.0 (CH_3), 86.5 (C), 91.1 (C), 114.3 (CH), 121.8 (C), 129.4 (CH), 160.8 (C), 164.0 (C), 169.5 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}INO_3^+$ 369.9935; Found 369.9929.

3-(4-Bromophenyl)-4-(3-iodoprop-2-yn-1-yl)-5-methoxyisoxazole 5c was obtained following the general procedure IVB from 3-(4-bromophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole **1e** (212 mg, 0.73 mmol) in 249 mg (82%) yield as a light-brown solid, mp 110-112 °C (water). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.39 (s, 2H), 4.16 (s, 3H), 7.58 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ -4.2 (C), 13.8 (CH_2), 58.1 (CH_3), 86.7 (C), 90.7 (C), 124.3 (C), 128.3 (C), 129.6 (CH), 132.1 (CH), 163.4 (C), 169.7 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{10}BrINO_2^+$ 417.8934; Found 417.8949.

4-(3-Cloroprop-2-yn-1-yl)-5-methoxy-3-phenylisoxazole 6. The solution of 5-methoxy-3-phenyl-4-(prop-2-yn-1-yl)isoxazole **1a** (320 mg, 1.5 mmol) in dry THF (10 mL) was treated with *n*-butyl lithium solution (2.5 M solution in hexane, 1.2 mL, 3.0 mmol) with stirring under argon atmosphere at -78 °C during 0.5 h. A *N*-chlorosuccinimide (268 mg, 3.0 mmol) solution in dry (THF 5.0 mL) was then added dropwise upon cooling, and stirring was continued allowing slow warming up to 0 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. Combined organic phases were washed with water, saturated aqueous sodium bicarbonate and brine and dried over anhydrous sodium sulfate. The volatiles were removed *in vacuo* and the residue was subjected to column chromatography on silica eluting with light petroleum/ethyl acetate (8/1) mixture to provide the product **6** in 136 mg (55 %) yield as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.25 (s, 2H), 4.17 (s, 3H), 7.46-7.50 (m, 3H), 7.66-7.71 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.9 (CH_2), 58.0 (CH_3), 66.5 (C), 86.6 (C), 128.0 (CH), 128.8 (CH), 129.4 (C), 129.8 (CH), 164.3 (C), 169.6 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{10}ClNNaO_2^+$ 270.0292; Found 270.0297.

5-Methoxy-3-(4-methylphenyl)-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole 10a. The solution of 5-methoxy-3-(4-methylphenyl)isoxazole[44] (380 mg, 2.0 mmol) in dry THF (10 mL) was treated dropwise with *n*-butyl lithium solution (2.5 M solution in hexane, 1.0 mL, 2.5 mmol) under argon atmosphere upon cooling at -78 °C with stirring and the mixture was stirred for 0.5 h at -70~-60 °C. Copper(I) cyanide (197 mg, 2.2 mmol) and triphenylphosphane (577 mg, 2.2 mmol) were added in one portion and the resulting mixture was stirred for further 15 minutes at -60 °C. (3-Bromoprop-1-yn-1-yl)trimethylsilane[45] (478 mg, 2.5 mmol) solution in dry THF (2 mL) was then added by syringe in one portion and the mixture was allowed to warm up gradually to 0 °C for 1.5 h and agitated at that temperature for one hour more. The reaction mixture was quenched with ice-cold aqueous ammonium chloride with aqueous ammonia addition and extracted with ethyl acetate. The organic phase was washed with aqueous ammonia, water and brine and dried over anhydrous sodium sulfate. All volatiles were removed *in vacuo* and the residue was subjected to column chromatography on silica eluting with light petroleum/ethyl acetate (10/1) mixture to provide the title product **10a** in 180 mg (30%) yield as an yellow oil along with 145 mg (38% recovery) of unreacted starting isoxazole. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.10 (s, 9H), 2.41 (s, 3H), 3.28 (s, 2H), 4.14 (s, 3H), 7.27 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ -0.16 (CH_3), 13.0 (CH_2), 21.4 (CH_3), 57.9 (CH_3), 85.4 (C), 87.3 (C), 103.5 (C), 126.7 (C), 128.0 (CH), 129.3 (CH), 139.7 (C), 164.5 (C), 169.4 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{21}NNaO_2Si^+$ 322.1234; Found 322.1250.

4-(3-(5-Methoxy-3-(4-methylphenyl)isoxazol-4-yl)prop-1-yn-1-yl)benzonitrile 12. 5-Methoxy-3-(4-methylphenyl)-4-(prop-2-yn-1-yl)isoxazole **1b** (227 mg, 1.0 mmol), 4-iodobenzonitrile (229 mg, 1.0 mmol), triphenylphosphane (53 mg, 0.2 mmol), calcined potassium carbonate (166 mg, 1.2 mmol), dry tetrabutylammonium iodide (37 mg, 0.1 mmol) and magnetic stirring bar were placed in a Schlenk flask and purged with argon. Degassed absolute DMF (5 mL) was added followed after 5 min. stirring with palladium acetate (11 mg, 0.05 mmol) and the mixture was heated under argon

atmosphere at 50 °C for 20 h. All volatiles were removed *in vacuo* and the residue was subjected to column chromatography on silica eluting with light petroleum/ethyl acetate (5/1) mixture to provide the cross-coupling product **12** (230 mg, 70 %) as a colorless solid mp 135-136 °C (light petroleum-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 3.51 (s, 2H), 4.18 (s, 3H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.7 (CH_2), 21.4 (CH_3), 58.0 (CH_3), 79.7 (C), 86.4 (C), 91.7 (C), 111.3 (C), 118.5 (C), 126.6 (C), 127.9 (CH), 128.3 (C), 129.5 (CH), 131.9 (CH), 132.1 (CH), 139.9 (C), 164.3 (C), 169.5 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{16}N_2NaO_2^+$ 351.1104; Found 351.1108.

General procedure V for the isomerization of isoxazoles to pyridines. Isoxazole (1 mmol) was dissolved in 1,2-dichloroethane (5 mL), iron(II) bis((trifluoromethyl)sulfonyl)amide (31 mg, 0.05 mmol, 5 mol%) and bis((trifluoromethyl)sulfonyl)amide [triphenylphosphane]gold(I) (37 mg, 0.05 mmol, 5 mol%) were added and the mixture was heated at 85°C in a screw-cap thick-wall tube for a period indicated in Tables 2 and 3. The reaction mixture was concentrated *in vacuo* and the product was purified by column chromatography on deactivated with triethylamine silica eluting with petroleum ether/ethyl acetate ~8/1 mixture.

Methyl 2-phenylnicotinate 3a was obtained following the general procedure V from 5-methoxy-3-phenyl-4-(prop-2-yn-1-yl)isoxazole **1a** (213 mg, 1.00 mmol) in 152 mg (71%) yield as a pale-yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (s, 3H), 7.33 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.41-7.47 (m, 3H), 7.52-7.56 (m, 2H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.78 (dd, *J* = 4.8, 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.3 (CH_3), 121.5 (CH), 127.0 (C), 128.1 (CH), 128.5 (CH), 128.7 (CH), 137.8 (CH), 140.0 (C), 151.3 (CH), 158.8 (C), 168.5 (C). Spectral data were in agreement with previously reported values.[46]

Methyl 2-(4-methylphenyl)nicotinate 3b was obtained following the general procedure V from 5-methoxy-3-(4-methylphenyl)-4-(prop-2-yn-1-yl)isoxazole **1b** (118 mg, 0.52 mmol) in 97 mg (82%) yield as a pale-yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 3.72 (s, 3H),

7.24 (d, J = 8.1 Hz, 2H), 7.30 (dd, J = 7.8, 4.8 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 8.06 (dd, J = 7.8, 1.7 Hz, 1H), 8.76 (dd, J = 4.8, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3 (CH_3), 52.3 (CH_3), 121.2 (CH), 126.8 (C), 128.4 (CH), 128.9 (CH), 137.1 (C), 137.7 (CH), 138.6 (C), 151.2 (CH), 158.7 (C), 168.7 (C). Spectral data were in agreement with previously reported values.[47]

Methyl 2-(4-methoxyphenyl)nicotinate 3c was obtained following the general procedure V from 5-methoxy-3-(4-methoxylphenyl)-4-(prop-2-yn-1-yl)isoxazole **1c** (50 mg, 0.22 mmol) in 47 mg (94%) yield as an yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 3H), 3.86 (s, 3H), 6.95-6.98 (m, 2H), 7.28 (dd, J = 7.8, 4.8 Hz, 1H), 7.50-7.53 (m, 2H), 8.05 (dd, J = 7.8, 1.8 Hz, 1H), 8.74 (dd, J = 4.8, 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.4 (CH_3), 55.3 (CH_3), 113.7 (CH), 121.0 (CH), 126.6 (C), 130.0 (CH), 132.4 (C), 137.80 (CH), 151.2 (CH), 158.2 (C), 160.2 (C), 168.9 (C). Spectral data were in agreement with previously reported values.[48]

Methyl 2-(4-chlorophenyl)nicotinate 3d was obtained following the general procedure V from 3-(4-chlorophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole **1d** (124 mg, 0.50 mmol) in 113 mg (91%) yield as a pale-yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 3H), 7.35 (dd, J = 7.8, 4.8 Hz, 1H), 7.38-7.44 (m, 2H), 7.45-7.51 (m, 2H), 8.12 (dd, J = 7.8, 1.7 Hz, 1H), 8.77 (dd, J = 4.8, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.4 (CH_3), 121.8 (CH), 126.7 (C), 128.3 (CH), 129.9 (CH), 134.9 (C), 138.0 (CH), 138.5 (C), 151.4 (CH), 157.7 (C), 168.1 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}ClNO_2^+$ 248.0473; Found 248.0477.

Methyl 2-(4-bromophenyl)nicotinate 3e was obtained following the general procedure V from 3-(4-bromophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole **1e** (100 mg, 0.34 mmol) in 90 mg (90%) yield as a colorless solid, mp 53-54.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 3H), 7.36 (dd, J = 7.8, 4.8 Hz, 1H), 7.40-7.44 (m, 2H), 7.56-7.59 (m, 2H), 8.12 (dd, J = 7.8, 1.7 Hz, 1H), 8.77 (dd, J = 4.8, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.4 (CH_3), 121.8 (CH), 123.2 (C), 126.7 (C), 130.2 (CH), 131.3 (CH), 138.1 (CH), 139.0 (C), 151.5 (CH), 157.7 (C), 168.1 (C). ^{1}H NMR spectral data were in good accordance with literature with exception that authors[49] missed to specify the

methyl group chemical shift. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}BrNO_2^+$ 291.9968; Found 291.9961.

Methyl 2-(3-bromophenyl)nicotinate 3f was obtained following the general procedure V from 3-(3-bromophenyl)-5-methoxy-4-(prop-2-yn-1-yl)isoxazole **1f** (60 mg, 0.20 mmol) in 40 mg (67%) yield as a light-yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 3H), 7.33 (dd, *J* = 7.9, 7.8 Hz, 1H), 7.40 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.46 (ddd, *J* = 7.8, 1.5, 1.1 Hz, 1H), 7.58 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.75 (dd, *J* = 2.1, 2.0 Hz, 1H), 8.16 (dd, *J* = 7.8, 1.7 Hz, 1H), 8.80 (dd, *J* = 4.8, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.4 (CH_3), 122.1 (CH), 122.2 (C), 126.9 (C), 127.2 (CH), 129.5 (CH), 131.6 (CH), 131.7 (CH), 138.1 (CH), 142.0 (C), 151.5 (CH), 157.3 (C), 168.0 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}BrNO_2^+$ 291.9968; Found 291.9972.

Methyl 2-(4-nitrophenyl)nicotinate 3g was obtained following the general procedure V from 5-methoxy-3-(4-nitrophenyl)-4-(prop-2-yn-1-yl)isoxazole **1g** (50 mg, 0.19 mmol) in 45 mg (90%) yield as an yellowish solid, mp 129-130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.74 (s, 3H), 7.45 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.67-7.71 (m, 2H), 8.23 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.29-8.32 (m, 2H), 8.82 (dd, *J* = 4.8, 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.6 (CH_3), 122.8 (CH), 123.3 (CH), 126.8 (C), 129.6 (CH), 138.5 (CH), 146.5 (C), 147.9 (C), 151.8 (CH), 157.1 (C), 167.2 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2O_4^+$ 259.0713; Found 259.0714.

Methyl 2-cyclopropylnicotinate 3h was obtained following the general procedure V (with 10 mol% gold(I) load) from 3-cyclopropyl-5-methoxy-4-(prop-2-yn-1-yl)-isoxazole **1h** (72 mg, 0.41 mmol) in 44 mg (61%) yield as a light-brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98-1.04 (m, 2H), 1.13-1.19 (m, 2H), 3.01 (tt, *J* = 8.2, 4.8 Hz, 1H), 3.95 (s, 3H), 7.05 (dd, *J* = 7.9, 4.7 Hz, 1H), 8.06 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.52 (dd, *J* = 4.7, 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.00 (CH_2), 14.2 (CH), 52.3 (CH_3), 119.4 (CH), 125.2 (C), 137.8 (CH), 151.9 (CH), 163.6 (C), 167.6 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{12}NO_2^+$ 178.0863; Found 178.0870.

Methyl 2-(*tert*-butyl)nicotinate 3i was obtained following the general procedure V with (10 mol% gold(I) load) from 3-(*tert*-butyl)-5-methoxy-4-(prop-2-yn-1-yl)-isoxazole **1i** (96 mg, 0.50 mmol) in 89 mg (93%) yield as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 9H), 3.91 (s, 3H), 7.13 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.8 Hz, 1H), 8.61 (dd, *J* = 4.7, 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.0 (CH_3), 39.3 (C), 52.5 (CH_3), 120.0 (CH), 127.9 (C), 136.4 (CH), 149.2 (CH), 165.1 (C), 170.8 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{16}NO_2^+$ 194.1176; Found 194.1181.

Methyl 6-bromo-2-phenylnicotinate 7a was obtained following the general procedure V from 4-(3-bromoprop-2-yn-1-yl)-5-methoxy-3-phenylisoxazole **3a** (220 mg, 0.75 mmol) in 155 mg (70%) yield as a pale-yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (s, 3H), 7.42-7.44 (m, 3H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.52-7.54 (m, 2H), 7.93 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.5 (CH_3), 125.9 (C), 126.1 (CH), 128.2 (CH), 128.6 (CH), 129.2 (CH), 138.5 (C), 140.0 (CH), 143.8 (C), 159.9 (C), 167.7 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}BrNO_2^+$ 291.9968; Found 291.9970.

Methyl 6-bromo-2-(4-methylphenyl)nicotinate 7b was obtained following the general procedure V from 4-(3-bromoprop-2-yn-1-yl)-5-methoxy-3-(4-methylphenyl)isoxazole **3b** (100 mg, 0.33 mmol) in 72 mg (72%) yield as a pale-yellow viscous oil that solidified upon standing to ivory-colored solid, mp 62-64 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 3.72 (s, 3H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3 (CH_3), 52.5 (CH_3), 125.7 (C), 125.7 (CH), 128.6 (CH), 128.9 (CH), 135.6 (C), 139.4 (C), 139.9 (CH), 143.7 (C), 159.8 (C), 168.0 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}BrNO_2^+$ 306.0124; Found 306.0127.

Methyl 6-bromo-2-(4-methoxyphenyl)nicotinate 7c was obtained following the general procedure V from 4-(3-bromoprop-2-yn-1-yl)-5-methoxy-3-(4-methoxyphenyl)isoxazole **3c** (300 mg, 0.93 mmol) in 160 mg (53%) yield as a colorless solid, mp 103-104 °C. ^{1}H NMR ($CDCl_3$, 400

MHz): δ 3.73 (s, 3H), 3.86 (s, 3H), 6.93-6.97 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.49-7.53 (m, 2H), 7.88 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.5 (CH_3), 55.3 (CH_3), 113.7 (CH), 125.4 (C), 125.4 (CH), 130.3 (CH), 130.9 (C), 140.0 (CH), 143.6 (C), 159.3 (C), 160.7 (C), 168.2 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{12}BrNNaO_3^+$ 343.9893; Found 343.9903.

Methyl 6-bromo-2-(4-chlorophenyl)nicotinate 7d was obtained following the general procedure V from 4-(3-bromoprop-2-yn-1-yl)-3-(4-chlorophenyl)-5-methoxyisoxazole **3d** (163 mg, 0.50 mmol) in 130 mg (80%) yield as a colorless solid mp 122-3 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 3H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.6 (CH_3), 125.6 (C), 126.4 (CH), 128.4 (CH), 130.1 (CH), 135.6 (C), 136.9 (C), 140.2 (CH), 144.0 (C), 158.7 (C), 167.4 (C). HRMS (ESI-TOF) m/z: $[M + Ag]^+$ Calcd for $C_{13}H_9AgBrClNO_2^+$ 431.8551; Found 431.8560.

Methyl 6-bromo-2-(4-bromophenyl)nicotinate 7e was obtained following the general procedure f V rom 3-(4-bromophenyl)-4-(3-bromoprop-2-yn-1-yl)-5-methoxyisoxazole **3e** (150 mg, 0.40 mmol) in 114 mg (75%) yield as a colorless solid, mp 112-113 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 3H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.6 (CH_3), 123.9 (C), 125.6 (C), 126.5 (CH), 130.4 (CH), 131.4 (CH), 137.4 (C), 140.2 (CH), 144.0 (C), 158.8 (C), 167.4 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_9Br_2NNaO_2^+$ 391.8892; Found 391.8905.

Methyl 6-bromo-2-(4-nitrophenyl)nicotinate 7f was obtained following the general procedure V from 4-(3-bromoprop-2-yn-1-yl)-5-methoxy-3-(4-nitrophenyl)isoxazole **3f** (200 mg, 0.60 mmol) in 159 mg (80%) yield as a colorless solid, mp 149-152 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.74 (s, 3H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.67-7.69 (m, 2H), 8.07 (d, *J* = 8.2 Hz, 1H), 8.29-8.31 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.8 (CH_3), 123.3 (CH), 125.7 (C), 127.5 (CH), 129.8 (CH), 140.5 (CH), 144.5 (C), 144.8 (C), 148.2 (C), 158.0 (C), 166.4 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_9BrN_2NaO_4^+$ 358.9638; Found 358.9651.

Methyl 6-bromo-2-methylnicotinate 7g was obtained following the general procedure V (with 7.5 mol% gold(I) load) from 4-(3-bromoprop-2-yn-1-yl)-5-methoxy-3-methylisoxazole **3g** (55 mg, 0.24 mmol) in 22 mg (40%) yield as an yellowish solid mp 31-33 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.82 (s, 3H), 3.92 (s, 3H), 7.40 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.6 (CH_3), 52.4 (CH_3), 124.4 (C), 125.4 (CH), 140.5 (CH), 144.4 (C), 161.7 (C), 166.2 (C). HRMS (ESI-TOF) m/z: $[M + Ag]^+$ Calcd for $C_8H_8AgBrNO_2^+$ 335.8784; Found 335.8806.

Methyl 6-bromo-2-cyclopropylnicotinate 7h was obtained following the general procedure V (with 7.5 mol% gold(I) load) from 4-(3-bromoprop-2-yn-1-yl)-3-cyclopropyl-5-methoxyisoxazole **3h** (220 mg, 0.86 mmol) in 100 mg (45%) yield as a light-yellow solid mp 35-36 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.02-1.08 (m, 2H), 1.17-1.22 (m, 2H), 3.03 (tt, *J* = 8.1, 4.8 Hz, 1H), 3.92 (s, 3H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.9 (CH_2), 14.3 (CH), 52.4 (CH_3), 123.8 (CH), 124.0 (C), 140.1 (CH), 145.0 (C), 165.9 (C), 166.8 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}BrNO_2^+$ 255.9968; Found 255.9969.

Methyl 6-bromo-2-(*tert*-butyl)nicotinate 7i was obtained following the general procedure V (with 7.5 mol% gold(I) load) from 4-(3-bromoprop-2-yn-1-yl)-3-(*tert*-butyl)-5-methoxyisoxazole **3i** (72 mg, 0.26 mmol) in 60 mg (83%) yield as a light-brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 9H), 3.90 (s, 3H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.8 (CH_3), 39.4 (C), 52.7 (CH_3), 124.5 (CH), 127.0 (C), 138.8 (CH), 141.4 (C), 167.0 (C), 169.8 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{15}BrNO_2^+$ 272.0281; Found 272.0278.

Methyl 6-iodo-2-phenylnicotinate 8a was obtained following the general procedure V from 4 (3-iodoprop-2-yn-1-yl)-5-methoxy-3-phenylisoxazole **4a** (135 mg, 0.40 mmol) in 119 mg (88%) yield as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.69 (s, 3H), 7.41-7.44 (m, 3H), 7.51-7.54 (m, 2H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.5 (CH_3),

120.2 (C), 126.2 (C), 128.2 (CH), 128.6 (CH), 129.2 (CH), 132.9 (CH), 138.6 (C), 138.8 (CH), 160.0 (C), 168.0 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{11}INO_2^+$ 339.9829; Found 339.9835.

Methyl 6-iodo-2-(4-methoxyphenyl)nicotinate 8b was obtained following the general procedure V from 4-(3-iodoprop-2-yn-1-yl)-5-methoxy-3-(4-methoxyphenyl)isoxazole **4b** (48 mg, 0.13 mmol) in 32 mg (67%) yield as a colorless solid, mp 100.5-101.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (s, 3H), 3.85 (s, 3H), 6.93-6.96 (m, 2H), 7.48-7.52 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.5 (CH_3), 55.3 (CH_3), 113.7 (CH), 120.1 (C), 125.7 (C), 130.2 (CH), 131.0 (C), 132.2 (CH), 138.7 (CH), 159.4 (C), 160.7 (C), 168.4 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}INO_3^+$ 369.9935; Found 369.9934.

Methyl 2-(4-bromophenyl)-6-iodo-nicotinate 8c was obtained following the general procedure V from 3-(4-bromophenyl)-4-(3-iodoprop-2-yn-1-yl)-5-methoxyisoxazole **4c** (174 mg, 0.42 mmol) in 124 mg (71%) yield as a colorless solid, mp 87-90 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.72 (s, 3H), 7.39-7.41 (m, 2H), 7.54-7.57 (m, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.6 (CH_3), 120.4 (C), 123.8 (C), 125.9 (C), 130.3 (CH), 131.4 (CH), 133.3 (CH), 137.5 (C), 139.0 (CH), 158.9 (C), 167.6 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_9BrINNaO_2^+$ 439.8754; Found 439.8768.

Methyl 6-chloro-2-phenylnicotinate 9 was obtained following the general procedure V from 4-(3-chloroprop-2-yn-1-yl)-5-methoxy-3-phenylisoxazole **5** (100 mg, 0.40 mmol) in 63 mg (63%) yield as an yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (s, 3H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.41-7.46 (m, 3H), 7.51-7.57 (m, 2H), 8.05 (d, *J* = 8.2 Hz, 1H). Spectral data were in agreement with previously reported values.[50] HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{10}ClNNaO_2^+$ 270.0292; Found 270.0295.

Methyl 2-(4-methylphenyl)-6-(trimethylsilyl)nicotinate 11a was obtained following the general procedure V from 5-methoxy-3-(4-methylphenyl)-4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazole **10a**

(112 mg, 0.37 mmol) in 17 mg (15%) yield as a colorless viscous oil along with methyl 2-(4-methylphenyl)nicotinate **3b** that aroused in the reaction as the main product 60 mg (70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.34 (s, 9H), 2.41 (s, 3H), 3.72 (s, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 7.7 Hz, 1H). The substance decayed in solution and upon storage, therefore no ^{13}C and mass-spectra of appropriate quality were recorded.

Methyl 6-(4-cyanophenyl)-2-(4-methylphenyl)nicotinate 13 was obtained following the general procedure V from 4-(3-(5-methoxy-3-(4-methylphenyl)isoxazol-4-yl)prop-1-yn-1-yl)benzonitrile **12** (100 mg, 0.30 mmol) for 16 h in 98 mg (98%) yield as a light-yellow solid mp 96-98 °C (hexane-EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.43 (s, 3H), 3.76 (s, 3H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 3H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3 (CH_3), 52.4 (CH_3), 113.1 (C), 118.0 (CH), 118.6 (C), 126.0 (C), 127.8 (CH), 128.6 (CH), 128.9 (CH), 132.5 (CH), 136.9 (C), 139.0 (C), 139.1 (CH), 142.3 (C), 156.0 (C), 158.8 (C), 168.5 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_2^+$ 329.1285; Found 329.1290.

Synthesis of 2,6-disubstituted nicotinates

Methyl 6-((4-chlorophenyl)sulfanyl)-2-(4-nitrophenyl)nicotinate 14. 4-Chlorothiophenole (38 mg, 0.26 mmol) was dissolved in dry THF (5 mL) and NaH (60% susp. in oil) (11 mg, 0.28 mmol) was then added. The mixture was stirred for 15 minutes, and a solution of methyl 6-bromo-2-(4-nitrophenyl)nicotinate **7f** (73 mg, 0.22 mmol) in dry THF (3 mL) was added. The mixture was stirred for 2 hours, and sodium 4-chlorothiophenolate (freshly prepared of 4-chlorothiophenole (38 mg, 0.26 mmol) and NaH (60% susp. in oil) (11 mg, 0.28 mmol) in dry THF (5 mL)) was added. After additional 2 hours the solvent was removed *in vacuo*, and the residue was purified by column chromatography (light petroleum/ethyl acetate 6/1 + 1% TEA) to give pure compound in 67 mg (89%) yield as an yellowish solid, mp 130-132 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (s, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H),

8.00 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 52.4 (CH_3), 119.2 (CH), 122.4 (C), 123.1 (CH), 127.7 (C), 129.8 (CH), 130.1 (CH), 136.4 (C), 136.8 (CH), 139.1 (CH), 145.9 (C), 147.9 (C), 157.2 (C), 165.0 (C), 166.8 (C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{13}ClN_2NaO_4S^+$ 423.0177; Found 423.0181.

Methyl 2-(4-bromophenyl)-6-(pyrrolidin-1-yl)nicotinate 15. A mixture of 6-bromo-2-(4-bromophenyl)nicotinate **7e** (33 mg, 0.1 mmol), pyrrolidine (71 mg, 1.0 mmol) and K_2CO_3 (21 mg, 0.15 mmol) in dry THF (3mL) was refluxed for 1.5 hours. All volatiles were removed *in vacuo*, and the residue was suspended in water and the solid formed was filtered off and dried in air to give 30 mg (96%) of pure product as a colorless solid, mp 120-122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.00-2.03 (m, 4H), 3.53 (br. s, 4H), 3.65 (s, 3H), 6.31 (d, J = 8.8 Hz, 1H), 7.34-7.43 (m, 2H), 7.46-7.54 (m, 2H), 8.00 (d, J = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 25.4 (CH_2), 46.8 (CH_2), 51.4 (CH_3), 104.1 (CH), 112.3 (C), 122.3 (C), 130.5 (CH), 130.7 (CH), 139.9 (CH), 140.7 (C), 157.3 (C), 159.3 (C), 168.0 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}BrN_2O_2^+$ 361.0546; Found 361.0551.

Methyl 6-(hex-1-yn-1-yl)-2-(4-methoxyphenyl)nicotinate 16. A mixture of methyl 6-bromo-2-(4-methoxyphenyl)nicotinate **7c** (80 mg, 0.25 mmol), CuI (1.9 mg, 10 μmol), $(PPh_3)_2PdCl_2$ (3.5 mg, 5 μmol) and PPh_3 (2.6 mg, 10 μmol) in dry triethylamine (3 mL) was stirred for 30 min. under argon atmosphere in a thick-wall screw cap tube. Hex-1-yne (20.5 mg, 0.25 mmol) was then added and the mixture was stirred for 1 day at ambient temperature. Saturated aqueous NH_4Cl was added to the reaction mixture and the product was extracted with ether, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (light petroleum/ethyl acetate 15:1 + 1% TEA) to give pure product in 80 mg (99%) yield as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, J = 7.3 Hz, 3H), 1.42-1.54 (m, 2H), 1.57-1.67 (m, 2H), 2.46 (t, J = 7.1 Hz, 2H), 3.71 (s, 3H), 3.84 (s, 3H), 6.92-6.99 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.47-7.51 (m, 2H), 7.98 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.6 (CH_3), 19.2 (CH_2), 22.1 (CH_2), 30.3 (CH_2), 52.3 (CH_3),

55.3 (CH_3), 80.4 (C), 93.4 (C), 113.5 (CH), 124.1 (CH), 124.8 (C), 130.1 (CH), 132.2 (C), 138.0 (CH), 145.5 (C), 158.7 (C), 160.2 (C), 168.5 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_3^+$ 324.1594; Found 324.1596.

Methyl 2-(4-chlorophenyl)-6-phenylnicotinate 17. A mixture of 6-bromo-2-(4-chlorophenyl)nicotinate **7d** (65 mg, 0.20 mmol), phenylboronic acid (37 mg, 0.30 mmol), $(PPh_3)_2PdCl_2$ (7 mg, 10 μmol) and K_2CO_3 (55 mg, 0.40 mmol) was refluxed in a mixture of THF/water (3:1, 3 mL) for 2 hours. After cooling, product was extracted with ether, the solvents were removed *in vacuo* and the residue was purified by column chromatography (light petroleum/ethyl acetate 15:1 + 1% TEA) to give pure product, 62 mg (97%), as a colorless solid, mp 100-101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.76 (s, 3H), 7.42-7.52 (m, 5H), 7.58-7.61 (m, 2H), 7.78 (d, J = 8.2 Hz, 1H), 8.11-8.13 (m, 2H), 8.20 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.3 (CH_3), 118.0 (CH), 124.6 (C), 127.3 (CH), 128.2 (CH), 128.8 (CH), 129.9 (CH), 130.2 (CH), 134.9 (C), 138.0 (C), 138.8 (C), 139.2 (CH), 157.6 (C), 158.7 (C), 168.2 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{15}ClNO_2^+$ 324.0786; Found 324.0794.

Methyl 2-([1,1'-biphenyl]-4-yl)-6-phenylnicotinate 18. A mixture of 6-bromo-2-(4-bromophenyl)nicotinate **7e** (70 mg, 0.19 mmol), phenylboronic acid (28 mg, 0.23 mmol), $(PPh_3)_2PdCl_2$ (7 mg, 9.5 μmol) and K_2CO_3 (53 mg, 0.38 mmol) was refluxed in a mixture of THF/water (3:1, 3 mL) for 15 hours, while $(PPh_3)_2PdCl_2$ (10.5 mg, 14.5 μmol) and phenylboronic acid (42 mg, 0.34 mmol) were added in two portions after each 5 hours of agitation. After cooling, product was extracted with ether, the solvents were removed *in vacuo* and the residue was purified by column chromatography (light petroleum/ethyl acetate 15:1 + 1% TEA) to give pure product, 54 mg (69%), as a colorless solid, mp 125-126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 3H), 7.36-7.40 (m, 1H), 7.44-7.53 (m, 5H), 7.67-7.77 (m, 6H), 7.79 (d, J = 8.2 Hz, 1H), 8.15-8.17 (m, 2H), 8.20 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 52.3 (CH_3), 117.8 (CH), 124.8 (C), 126.8 (CH), 127.2 (CH), 127.3 (CH), 127.5 (CH), 128.8 (CH), 128.8 (CH), 129.3 (CH), 129.8 (CH), 138.2

(C), 139.0 (CH), 139.2 (C), 140.7 (C), 141.5 (C), 158.3 (C), 158.6 (C), 168.7 (C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{20}NO_2^+$ 366.1489; Found 366.1491.

Supporting Information. Copies of ^1H NMR spectra for all compounds synthesized; copies of ^1H, ^{13}C NMR and DEPT spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

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ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of the Russian Foundation for Basic Research (Grant No. 16-33-00695) and Saint Petersburg State University (Grant No. 12.38.217.2015). This research was carried out using resources of the Centre for Magnetic Resonance and the Centre for Chemical Analysis and Materials of Saint Petersburg State University.

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