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Iodocyclization of Hydroxylamine Derivatives Based on the Control of Oxidative Aromatization Leading to 2,5-Dihydroisoxazoles and Isoxazoles

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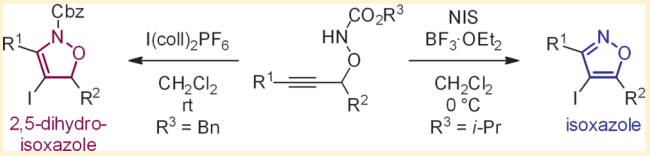
Supporting Information

ABSTRACT: An efficient method for the synthesis of 2,5-dihydroisoxazoles and isoxazoles using iodocyclization of *N*-alkoxycarbonyl *O*-propargylic hydroxylamines has been developed. 2,5-Dihydro-4-iodoisoxazole underwent the cross-coupling reactions without aromatization to afford polyfunctionalized 2,5-dihydroisoxazoles. This process was applied to the preparation of valdecoxib and its 2,5-dihydro-derivative.



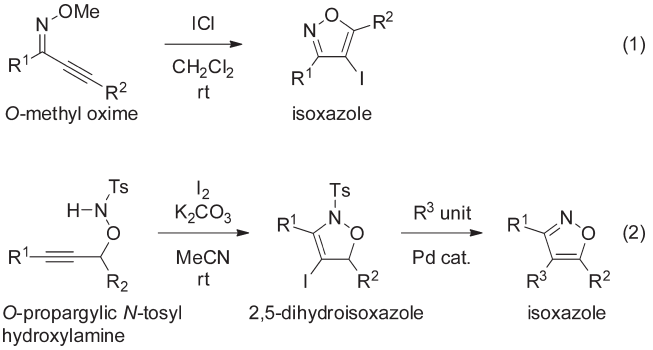
INTRODUCTION

Isoxazoles and their dihydro-derivatives are well-known to possess widespread biological activities.[1,2] Due to their attractive properties, numerous synthetic approaches for the construction of the isoxazole framework have been reported.[3] Although the preparation of 2,3- and 4,5-dihydroisoxazoles has been well established,[4] that of 2,5-dihydoroisoxazoles (3-isoxazolines) is rare and only monosubstituted variants have been synthesized.[5] Therefore, alternative methods for the preparation of polysubstituted 2,5-dihydroisoxazoles are desirable.

Iodocyclization, one of the most useful methods for the construction of functionalized ring systems,[6,7] creates cyclic architectures along with an iodo-functionality in the same molecule so that the reaction products can undergo further transformations. Iodine reagents have recently attracted much attention by organic chemists due to their environmentally friendly properties and low cost as applied toward eco-technologies.

Larock and colleagues reported an efficient synthesis of 4-iodoisoxazoles via iodocyclization from 2-alkyn-1-one *O*-methyl oximes (Scheme 1, eq 1).[8] The requisite 2-alkyn-1-one required for their methodology can be readily synthesized, and demonstrated iodocyclizations proceeded in mild conditions. Recently, Knight and co-workers presented an elegant approach toward 2,5-dihydro-4-iodoisoxazoles by iodocyclization of *O*-propargylic *N*-tosyl hydroxylamines (Scheme 1, eq 2).[9] During the palladium-catalyzed coupling reactions toward the iodine atom bonded to an sp^2-carbon, *N*-tosyl-2,5-dihydroisoxazoles were easily aromatized to isoxazoles along with the elimination of the *p*-tosyl group due to their basic conditions. Therefore, this method could be adapted to the construction of a compound library of isoxazoles, however, that of 2,5-dihydro-derivatives has not been achieved yet. Consequently, we sought an efficient approach to both isoxazoles and dihydroisoxazoles with enhanced potential for functionalizaions.

Scheme 1. Previous Method for the Synthesis of Isoxazoles and 2,5-Dihydroisoxazoles by Iodocyclization



We recently reported a switchable access to 2,5-dihydropyrazoles and pyrazoles through the iodocyclization of propargylic hydrazides as common substrates (Scheme 2, eq 1).[10] Our methodology is based on the control of oxidative aromatization by the iodocyclization reaction conditions so that diverse approaches to the desired cyclic compounds are allowed.[11] We thought that this strategy could be adapted to other substrates if appropriate precursors and reaction conditions for cyclization were designed. Herein we wish to report an iodocyclization of *N*-alkoxycarbonyl *O*-propargylic hydroxylamine derivatives leading to 2,5-dihydroisoxazoles and isoxazoles in connection with our recent explorations of the 5-*endo*-*dig* type iodocyclizations (Scheme 2, eq 2).[12] Our developed strategy have some advantages over previous method: first, switchable access to 2,5-dihydroisoxazole and isoxazole was enabled, second, the cross-coupling

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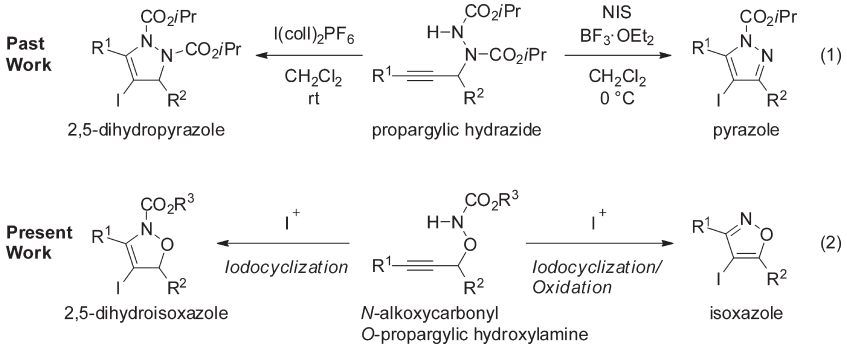
Scheme 2. Our Strategy for the Synthesis of Isoxazole and 2,5-Dihydroisoxazole by Iodocyclization



Scheme 3. Preparation of the Precursors

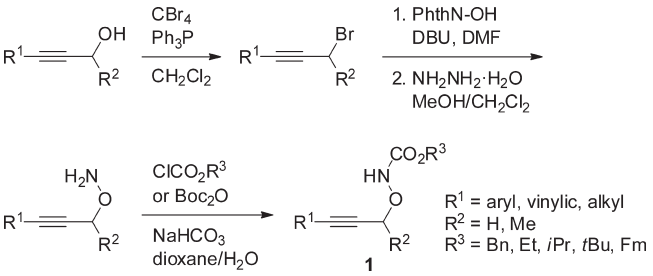
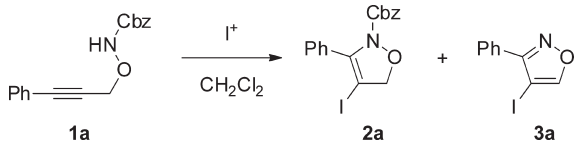


Table 1. Optimization of Reaction Conditions[a]



entry	[I+] source (equiv)	additive[b]	T (°C)	time (min)	yield (%) 2a	yield (%) 3a
1	**I(coll)$_2$PF$_6$ (1.5)**	**none**	**rt**	**30**	**97**	**0**
2	I(coll)$_2$PF$_6$ (2.5)	none	rt	15	90	0
3	I(coll)$_2$PF$_6$ (2.5)	$BF_3\cdot OEt_2$	rt	60	35	9
4	NIS (2.5)	none	rt	60	69	0
5	NIS (2.5)	$BF_3\cdot OEt_2$	rt	15	0	39
6	**NIS (2.5)**	**$BF_3\cdot OEt_2$**	**0**	**15**	**0**	**48**
7	I_2 (2.5)	$NaHCO_3$	rt	120	0	43
8	ICl (2.5)	none	rt	15	0	21

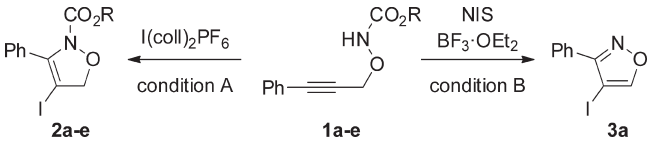
[a] Reaction was performed in CH_2Cl_2 (0.1 M) under argon atmosphere. [b] Equivalents of additive are the same as that of [I+].

reactions of 2,5-dihydro-4-iodoisoxazoles were underwent without aromatization to afford polyfunctionalized 2,5-dihydroisoxazoles. This process was applied to the preparation of valdecoxib and its 2,5-dihydro-derivatives.

RESULTS AND DISCUSSION

The *N*-alkoxycarbonyl *O*-propargylic hydroxylamines **1** required for our studies were prepared in the four-step sequence from propargylic alcohols (Scheme 3).[13] In brief, the respective four steps comprising bromination of propargylic alcohols, *O*-alkylation of *N*-hydroxyphthalimide, removal of phthalimide, and protection of the nitrogen atom by carbamate were performed to give **1** in good yields.

Table 2. Optimization of Carbamate Groups



entry	substrate	R	condition[a]	time (min)	product	yield (%)
1	**1a**	**Bn**	**A**	**30**	**2a**	**97**
2	**1b**	Et	A	30	**2b**	<29[b]
3	**1c**	*i*-Pr	A	30	**2c**	87
4	**1d**	*t*-Bu	A	30	**2d**	67
5	**1e**	Fm[c]	A	20	**2e**	94
6	**1a**	Bn	B	15	**3a**	48
7	**1b**	Et	B	20	**3a**	56
8	**1c**	***i*-Pr**	**B**	**20**	**3a**	**63**
9	**1d**	*t*-Bu	B	15	**3a**	57
10	**1e**	Fm[c]	B	15	**3a**	38

[a] Condition A: I(coll)$_2$PF$_6$ (1.5 equiv), CH_2Cl_2 (0.1 M), rt; Condition B: NIS (2.5 equiv), $BF_3\cdot OEt_2$ (2.5 equiv), CH_2Cl_2 (0.1 M), 0 °C. [b] Product **2b** was unstable. [c] Fm = 9-fluorenylmethyl.

We first scrutinized the reaction of **1a** toward the iodinating reagents (Table 1). According to our previous work,[10] bis(2,4,6-collidine)iodonium(I) hexafluorophosphate [I(coll)$_2$PF$_6$][14] was examined as the first choice for an iodinating reagent to give 2,5-dihydroisoxazole **2a** in excellent yield (entry 1). I(coll)$_2$PF$_6$ (1.5 equiv) alone was sufficient for the synthesis of **2a**, and the use of an activator of the iodinating reagent such as $BF_3\cdot OEt_2$ or *N*-iodosuccinimide (NIS) in place of I(coll)$_2$PF$_6$ caused a diminishment of the yields of **2a** (entries 2−4). Notably, the combination of NIS/$BF_3\cdot OEt_2$ afforded isoxazole **3a** as the sole product in moderate yield (entry 5). When the reaction temperature was decreased to 0 °C, the yield of **3a** improved to 48% (entry 6). We examined other iodinating reagents, but lower yields of **3a** were observed (entries 7, 8).

Next, we investigated the effect of the carbamate groups (Table 2). Among the carbamate groups, benzyloxycarbonyl (Cbz, R = Bn) was the most suitable for the synthesis of

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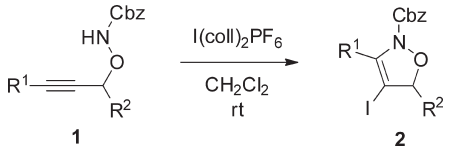
Table 3. Synthesis of 2,5-Dihydroisoxazole 2 by Iodocyclization of 1[a]



1 2

entry	substrate 1	R^1	R^2	time (min)	product	yield (%)
1	**1f**	*o*-MeC_6H_4	H	20	**2f**	93
2	**1g**	*p*-MeC_6H_4	H	20	**2g**	89
3	**1h**	*o*-$MeOC_6H_4$	H	20	**2h**	95
4	**1i**	*m*-$MeOC_6H_4$	H	20	**2i**	98
5	**1j**	*p*-$MeOC_6H_4$	H	20	**2j**	80
6	**1k**	*o*-$NO_2C_6H_4$	H	20	**2k**	75
7	**1l**	*m*-$NO_2C_6H_4$	H	20	**2l**	81
8	**1m**	*p*-$NO_2C_6H_4$	H	30	**2m**	87
9	**1n**	1-naphthyl	H	20	**2n**	95
10	**1o**	2-thienyl	H	30	**2o**	96
11	**1p**	1-cyclohexenyl	H	20	**2p**	80
12	**1q**	*n*-Bu	H	30	**2q**	94
13	**1r**	Ph	Me	20	**2r**	<96[b]

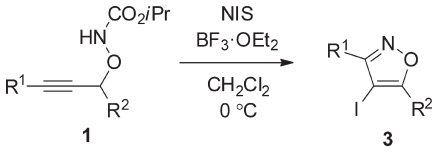
[a] Conditions: $I(coll)_2PF_6$ (2 equiv), CH_2Cl_2 (0.1 M), rt. [b] Product **2r** was unstable.

2,5-dihydroisoxazole **2** under condition A ($I(coll)_2PF_6$, CH_2Cl_2, rt; entries 1−5). In contrast, isopropyloxycarbonyl (R = *i*Pr) was the best choice for producing isoxazole **3** under condition B (NIS, $BF_3\cdot OEt_2$, CH_2Cl_2, 0 °C; entries 6−10).

Once the optimized conditions and *N*-protecting groups were established as in entries 1 and 8 (Table 2), various substrates were examined. The transformations from *N*-benzyloxycarbonyl *O*-propargylic hydroxylamines **1f**−**r** to 2,5-dihydroisoxazoles **2f**−**r** are summarized in Table 3. Our investigated conditions permitted a variety of substituents R^1 on the alkyne to afford the corresponding cyclized products in high yields. The presence of electron-donating or withdrawing substituents on the aromatic core did not influence the iodocyclizations (entries 1−9). As other sp^2-carbon centers for the substituent on the alkyne, heteroaromatic and vinylic groups were allowed (entries 10−11). It is noteworthy that alkyl- (sp^3 carbon center) substituted alkyne **1q** was also applicable in these conditions (entry 12). In addition, the iodocyclization proceeded in the presence of substituent R^2 at the propargylic position, however, cyclized product **2r** was unstable and slowly decomposed (entry 13). To our delight, *N*-isopropyloxycarbonyl *O*-propargylic hydroxylamines **1s**−**ae**, analogs of **1f**−**r**, also behaved as applicable substrates for the construction of isoxazoles **3s**−**ae** (Table 4). Compounds **1s**−**ae** cleanly underwent electrophilic cyclization to provide the respective products **3s**−**ae** in moderate to good yields. The presence of a nitro group on the aromatic core substituted at the alkynes required prolongation of reaction time to consume the substrates **1x**−**z** (entries 6−8, Table 4). Although iodocyclization of *n*-butyl-substituted alkyne **1ad** afforded **3ad** in 53% yield, further iodinated product **3ad′** was formed in 16% yield as inseparable mixture from **3ad** (entry 12).

To clarify the reaction mechanism, 2,5-dihydroisoxazole **2a** was treated with the combine reagent NIS/$BF_3\cdot OEt_2$ to afford

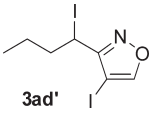
Table 4. Synthesis of Isoxazole 3 by Iodocyclization of 1[a]



1 3

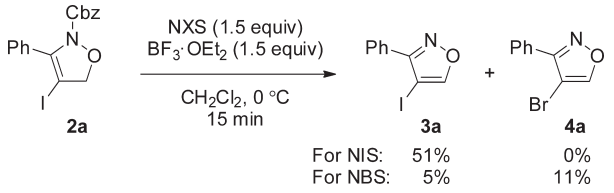
entry	substrate 1	R^1	R^2	time (min)	product	yield (%)
1	**1s**	*o*-MeC_6H_4	H	15	**3s**	71
2	**1t**	*p*-MeC_6H_4	H	15	**3t**	59
3	**1u**	*o*-$MeOC_6H_4$	H	15	**3u**	80
4	**1v**	*m*-$MeOC_6H_4$	H	15	**3v**	58
5	**1w**	*p*-$MeOC_6H_4$	H	15	**3w**	70
6	**1x**	*o*-$NO_2C_6H_4$	H	45	**3x**	50
7	**1y**	*m*-$NO_2C_6H_4$	H	45	**3y**	71
8	**1z**	*p*-$NO_2C_6H_4$	H	45	**3z**	62
9	**1aa**	1-naphthyl	H	30	**3aa**	79
10	**1ab**	2-thienyl	H	15	**3ab**	45
11	**1ac**	1-cyclohexenyl	H	15	**3ac**	66
12	**1ad**	*n*-Bu	H	30	**3ad**	53[b]
13	**1ae**	Ph	Me	15	**3ae**	96

[a] Conditions: NIS (2.5 equiv), $BF_3\cdot OEt_2$ (2.5 equiv), CH_2Cl_2 (0.1 M), 0 °C. [b] Product **3ad′** was also obtained in 16% yield and could not be separated from **3ad**.



3ad'

Scheme 4. Halonium Ion-Mediated Oxidation of 2,5-Dihydroisoxazole 2a to Isoxazole 3a and 4a



2a **3a** **4a**

	3a	**4a**
For NIS:	51%	0%
For NBS:	5%	11%

isoxazole **3a** in 51% yield (Scheme 4). This result indicated that the formation of isoxazole **3** from precursor **1** underwent via 2,5-dihydroisoxazole **2**. To understand precise mechanism of oxidative aromatization, we next examined the treatment of **2a** with the *N*-bromosuccinimide (NBS)/$BF_3\cdot OEt_2$ combination instead of NIS to afford 4-bromoisoxazole **4a** accompanied with **3a** in low yields due to its dirty reaction. However, this observation suggested that isoxazole **3** was formed via electrophilic addition of halonium ion to 2,5-dihydroisoxazole **2**.

Based on the outcomes of these reactions, we devised a plausible reaction mechanism for the iodocyclization (Scheme 5). The electrophilic 5-*endo-dig* cyclization of iodonium ion **A** gives dihydroisoxazole **2**. When more acidic conditions, NIS/$BF_3\cdot OEt_2$ system, are employed, more reactive I^+ species react on the π C−C double bond of the enecarbamate moiety to produce

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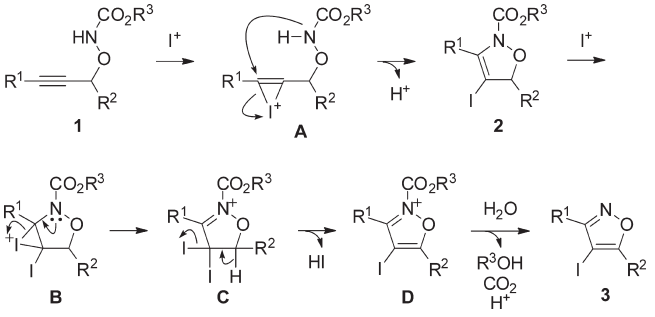
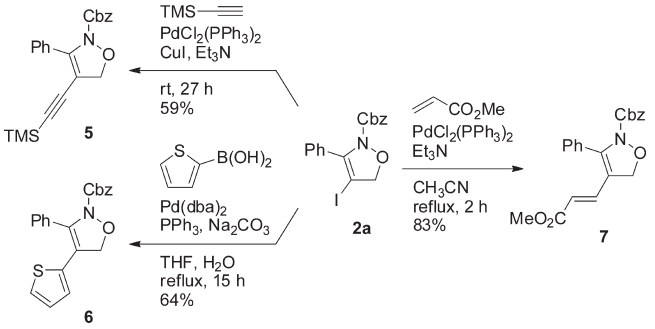
Scheme 5. Plausible Reaction Mechanism



Scheme 6. Transformation of 2,5-Dihydroisoxazole 2a



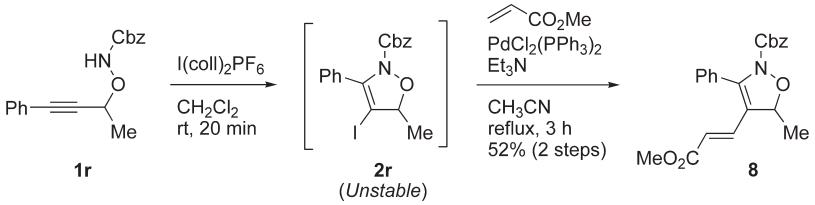
iodonium ion **B**. The ring-opening of **B** followed by elimination of HI from **C** affords *N*-alkoxycarbonyl isoxazolium ion **D**. Finally, H_2O-workup would cause hydrolysis to obtain isoxazole **3**. We considered that $I(coll)_2PF_6$ or NIS alone, weak iodonium sources, could not react with enecarbamate group of **2** so that their conditions afforded **2** as a sole product (Table 1, entries 1−6).

As discussed above, preparing substituted 2,5-dihydroisoxazoles was a challenging process due to the scope of substrates[5] or their tendency to easily oxidize to isoxazoles under cross-coupling conditions.[9] This rare class of heterocycles, the 2,5-dihydroisoxazoles, would be attractive for drug discovery, so we attempted the functionalization at the C−I bond of **2a** by using three palladium-catalyzed C−C bond forming reactions (Scheme 6). We performed Sonogashira coupling,[15] Suzuki−Miyaura cross-coupling,[16] and Mizoroki−Heck reaction[17] to afford the respective carbo-skeleton-assembled 2,5-dihydroisoxazoles **5**, **6**, and **7** in good yields without aromatization. Particularly, the Cbz group of **2a** was well tolerated under these conditions to prevent the 2,5-dihydroisoxazole from aromatizing.

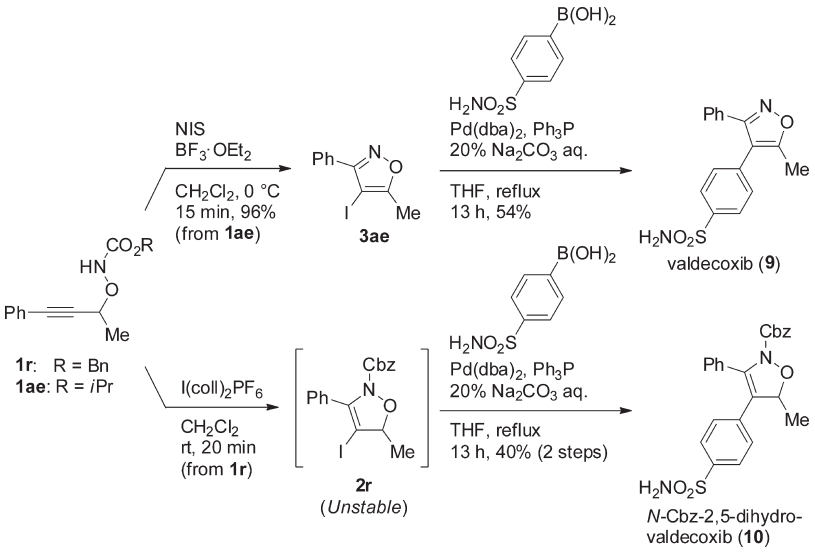
In addition, the unstable **2r** could also use in subsequent reaction to obtain polysubstituted 2,5-dihydroisoxazole **8** as the stable product in 52% yield from **1r** for two steps (Scheme 7).

With the general approach for the highly functionalized isoxazoles, the application of this method to the switchable synthesis of valdecoxib (**9**) and its 2,5-dihydro-derivative **10** was next examined (Scheme 8). Valdecoxib is a cyclooxigenase-2 (COX-2) selective inhibitor and was used for a nonsteroidal anti-inflammatory drug (NSAID) to treat osteoarthritis, rheumatoid

Scheme 7. Two-Step Preparation of Polysubstituted 2,5-Dihydroisoxazole 8



Scheme 8. Synthesis of Valdecoxib (9) and its 2,5-Dihydro Derivative 10



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arthritis, and painful menstruation.[18] Valdecoxib (**9**) was easily accessed from *N*-isopropyloxycarbonyl-*O*-propargylic hydroxylamine **1ae** in two steps; NIS/$BF_3 \cdot OEt_2$-mediated tandem iodocyclization/oxidation process of **1ae** produced isoxazole **3ae** in 96% yield, and subsequent Suzuki-Miyaura cross-coupling[16] with commercially available 4-sulphamoylbenzeneboronic acid afforded valdecoxib (**9**) in 54% yield. Similarly, *N*-Cbz-2,5-dihydro-vardecoxib (**10**) was synthesized in 40% overall yield from the precursor **1r** by $I(coll)_2PF_6$-promoted electrophilic iodocyclization and palladium-catalyzed cross-coupling sequence. As our methodology allowed not only the substituent diversity but also the choice of skeleton, a wide variety of analogs of valdecoxib (**9**) could be provided.

CONCLUSION

In summary, we developed an alternative method for the preparation of 2,5-dihydroisoxazoles and isoxazoles by iodocyclization of *N*-alkoxycarbonyl *O*-propargylic hydroxylamines. Our strategy takes advantage of the dual nature of iodine as both an iodinating and an oxidizing agent. Therefore, the control of the oxidative aromatization by the reaction conditions enabled 'product switch' and enhanced the flexibility of the synthetic route. In addition, the iodo moiety of the cyclized product **2** could create a variety of 2,5-dihydroisoxazoles, which may be difficult to prepare by other reported methods. As our methodology could be applied for the synthesis of valdecoxib and its 2,5-dihydro-analog, this research would be a valuable tool for drug discovery.

EXPERIMENTAL SECTION

General. IR spectra were measured using $CHCl_3$. Chemical shifts (δ) of ^1H NMR and ^{13}C NMR spectra are reported in ppm relative to tetramethylsilane as internal reference ($CDCl_3$: δ = 0 ppm for ^1H) and residual solvent signals ($CDCl_3$: δ = 77 ppm for ^{13}C; CD_3OD: δ = 3.31 and 49.0 ppm for ^1H and ^{13}C). *J*-Values are given in Hz.

General Procedure for the Preparation of *N*-Alkoxycarbonyl *O*-Propargylic Hydroxylamine 1. Step 1: According to literature,[19] CBr_4 (1.2 equiv) was added in one portion to a solution of propargylic alcohol (1 equiv) in dry CH_2Cl_2 (0.6 M) at 0 °C and the reaction was stirred at 0 °C. After 10 min, a solution of Ph_3P (1.5 equiv) in CH_2Cl_2 (1.5 M) was added via cannula and stirred at 0 °C for 10 min. Then the reaction mixture was allowed to warm at rt and further stirred for 1−1.5 h. After reaction completed, the mixture was evaporated in *vacuo*. The residue was purified by flash column chromatography on silica gel to give propargylic bromide. 3-Bromo-1-(2-methoxyphenyl)-1-propyne (for **1h** and **1u**) and 3-bromo-1-(1-naphthyl)-1-propyne (for **1n** and **1aa**) were prepared according to ref.19. 3-Bromo-1-phenyl-1-propyne (for **1a**−**e**), 3-bromo-1-(3-methoxyphenyl)-1-propyne (for **1i** and **1v**), and 1-bromo-2-heptyne (for **1q** and **1ad**) were prepared by the reaction of 3-phenyl-2-propyn-1-ol, 3-(3-methoxylphenyl)-2-propyn-1-ol, and 2-heptyn-1-ol with Br_2 and Ph_3P according to literature.[20,21] **Step 2:** According to literature,[13] DBU (1 equiv) was added dropwise to a solution of *N*-hydroxyphthalimide (1 equiv) and propargylic bromide (1 equiv) in DMF (0.2 M) at rt and stirred for 20−60 min. After reaction completed, the reaction mixture was poured into 1 M HCl (16.1 mL/mol), stirred for further 20 min. The resulting precipitated crystals were filtered, washed with water and the residue was dried to afford *O*-propargylic phthalimide, which was used without further purification for next reaction. Hydrazine monohydrate (1.05 equiv) was added to a solution of *O*-propargylic phthalimide (1 equiv) in MeOH/CH_2Cl_2 (1/1; 0.17 M) at rt, and stirred for 2.5−3 h. After reaction completed, the reaction mixture was poured into an aqueous solution of 2% H_2SO_4 (17 mL/mol), added CH_2Cl_2 (4.4 mL/mol), and stirred for 15−20 min. The mixture was filtered through a short Celite pad to remove the precipitate and the filter cake was washed with an aqueous solution of 2% H_2SO_4. The filtrate was extracted with CH_2Cl_2 and the remaining aqueous layer was neutralized with the addition of crystals $NaHCO_3$. The neutralized aqueous solution was then again extracted with CH_2Cl_2 and the combined organic layer was dried over Na_2SO_4 and evaporated in *vacuo*. The residue was purified by flash column chromatography on silica gel to give *O*-propargylic hydroxylamine. **Step 3:** According to literature,[22] $NaHCO_3$ (2 equiv) was added to a solution of *O*-propargylic hydroxylamine (1 equiv) in 1,4-dioxane/H_2O (1/1; 0.17 M) at rt and the mixture was stirred for 30 min. Then, alkyl chloroformate or Boc_2O (1.2 equiv) was added dropwise and stirred for 1 h. After reaction completed, the mixture was evaporated to its half volume in *vacuo*. The mixture was diluted with water and extracted with AcOEt. The organic layer was dried over Na_2SO_4, filtered and evaporated in *vacuo*. The residue was purified by flash column chromatography on silica gel to give *N*-alkoxycarbonyl *O*-propargylic hydroxylamine **1**.

*Benzyl(3-phenyl-2-propynyl)oxycarbamate (**1a**).* According to **step 2**, *O*-(3-phenyl-2-propynyl)hydroxylamine (2.16 g, 71% in 2 steps) was obtained from 3-bromo-1-phenyl-1-propyne[20] (4.00 g, 20.5 mmol). Eluent: hexane/Et_2O = 1/1. Colorless oil; IR ν_{max}: 3331, 3018, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2H), 7.32−7.28 (m, 3H), 5.62 (br s, 2H), 4.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.2, 128.4, 128.2, 122.4, 86.2, 84.7, 64.0; EI-HRMS calcd for C_9H_9NO (M^+) 147.0684. Found 147.0679. According to **step 3**, **1a** (185 mg, 96%) was obtained from *O*-(3-phenyl-2-propynyl)hydroxylamine (100 mg, 0.679 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 82−83 °C (hexane/CH_2Cl_2); IR ν_{max}: 3384, 3023, 2958, 1748, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (br s, 1H), 7.45−7.42 (m, 2H), 7.37−7.30 (m, 8H), 5.21 (s, 2H), 4.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 135.4, 131.8, 128.8, 128.6, 128.4, 128.3, 122.0, 87.7, 83.0, 67.7, 64.7; EI-HRMS calcd for $C_{17}H_{15}NO_3$ (M^+) 281.1052. Found 281.1067.

*Isopropyl(3-phenyl-2-propynyl)oxycarbamate (**1c**).* According to **step 3**, **1c** (154 mg, 98%) was obtained from *O*-(3-phenyl-2-propynyl)hydroxylamine (100 mg, 0.679 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 39 °C (hexane); IR ν_{max}: 3386, 2986, 1743, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (br s, 1H), 7.48−7.44 (m, 2H), 7.35−7.29 (m, 3H), 5.02 (sept, *J* = 6.3 Hz, 1H), 4.72 (s, 2H), 1.28 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 131.8, 128.7, 128.3, 122.1, 87.4, 83.2, 70.0, 64.6, 21.9; EI-HRMS calcd for $C_{13}H_{15}NO_3$ (M^+) 233.1052. Found 233.1070.

*Benzyl(3-(2-methylphenyl)-2-propynyl)oxycarbamate (**1f**).* According to **step 1**, 3-bromo-1-(2-methylphenyl)-1-propyne (1.68 g, 88%) was obtained from 3-(2-methylphenyl)-2-propyn-1-ol[20] (1.33 g, 9.09 mmol). Eluent: hexane. Colorless oil; IR ν_{max}: 2954, 2218, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.26−7.09 (m, 3H), 4.20 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 132.1, 129.5, 128.9, 125.5, 121.9, 88.0, 85.8, 20.6, 15.4; EI-HRMS calcd for $C_{10}H_9Br$ (M^+) 207.9888. Found 207.9891. According to **step 2**, *O*-(3-(2-methylphenyl)-2-propynyl)hydroxylamine (424 mg, 34% in 2 steps) was obtained from 3-bromo-1-(2-methylphenyl)-1-propyne (1.65 g, 7.88 mmol). Eluent: hexane/Et_2O = 1/1. Colorless oil; IR ν_{max}: 3330, 3016, 1579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.23−7.09 (m, 3H), 5.62 (br s, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 132.1, 129.4, 128.5, 125.5, 122.2, 88.5, 85.2, 64.2, 20.6; EI-HRMS calcd for $C_{10}H_{11}NO$ (M^+) 161.0841. Found 161.0829. According to **step 3**, **1f** (174 mg, 89%) was obtained from *O*-(3-(2-methylphenyl)-2-propynyl)hydroxylamine (106 mg, 0.657 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 55−56 °C (hexane/CH_2Cl_2); IR ν_{max}: 3385, 3022, 1748, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.41−7.30 (m, 6H), 7.25−7.09 (m, 3H), 5.20 (s, 2H), 4.76 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0,

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140.5, 135.4, 132.2, 129.4, 128.8, 128.6, 128.4, 128.3, 125.5, 121.8, 86.7, 86.6, 67.7, 64.9, 20.6; ESI-HRMS calcd for $C_{18}H_{18}NO_3$ ($M + H^+$) 296.1287. Found 296.1275.

*Benzyl(3-(4-methylphenyl)-2-propynyl)oxycarbamate (**1g**).* According to **step 1**, 3-bromo-1-(4-methylphenyl)-1-propyne (1.75 g, 76%) was obtained from 3-(4-methylphenyl)-2-propyn-1-ol[20] (1.59 g, 10.9 mmol). Eluent: hexane/Et_2O = 19/1. Colorless oil; IR ν_{max}: 3016, 2219, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.16 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 131.8, 129.1, 119.0, 87.0, 83.5, 21.5, 15.8; EI-HRMS calcd for $C_{10}H_9Br$ (M^+) 207.9888. Found 207.9900. According to **step 2**, *O*-(3-(4-methylphenyl)-2-propynyl)hydroxylamine (0.980 g, 74% in 2 steps) was obtained from 3-bromo-1-(4-methylphenyl)-1-propyne (1.71 g, 8.17 mmol). Eluent: hexane/Et_2O = 1/1. Colorless oil; IR ν_{max}: 3331, 3015, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 5.61 (br s, 2H), 4.51 (s, 2H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 131.7, 129.0, 119.3, 86.4, 83.9, 64.1, 21.3; EI-HRMS calcd for $C_{10}H_{11}NO$ (M^+) 161.0841. Found 161.0861. According to **step 3**, **1g** (226 mg, 92%) was obtained from *O*-(3-(4-methylphenyl)-2-propynyl)hydroxylamine (133 mg, 0.825 mmol). Eluent: hexane/Et_2O = 1/1. Colorless crystals; mp 82 °C (hexane/CH_2Cl_2); IR ν_{max}: 3385, 3022, 1748, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.39−7.31 (m, 7H), 7.10 (d, J = 7.8 Hz, 2H), 5.19 (s, 2H), 4.70 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 139.0, 135.4, 131.8, 129.0, 128.6, 128.4, 128.3, 118.9, 87.8, 82.3, 67.6, 64.9, 21.4; ESI-HRMS calcd for $C_{18}H_{18}NO_3$ ($M + H^+$) 296.1287. Found 296.1277.

*Benzyl(3-(2-methoxylphenyl)-2-propynyl)oxycarbamate (**1h**).* According to **step 2**, *O*-(3-(2-methoxyphenyl)-2-propynyl)hydroxylamine (857 mg, 99% in 2 steps) was obtained from 3-bromo-1-(2-methoxyphenyl)-1-propyne[19] (1.10 g, 4.88 mmol). Eluent: hexane/Et_2O = 3/2. Colorless oil; IR ν_{max}: 3331, 3018, 1581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.5, 1.8 Hz, 1H), 7.32−7.27 (m, 1H), 6.93−6.86 (m, 2H), 5.64 (br s, 2H), 4.57 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 133.7, 129.9, 120.3, 111.54, 110.49, 88.6, 82.8, 64.4, 55.7; CI-HRMS calcd for $C_{10}H_{12}NO_2$ ($M+H^+$) 178.0863. Found 178.0870. According to **step 3**, **1h** (293 mg, 88%) was obtained from *O*-(3-(2-methoxyphenyl)-2-propynyl)hydroxylamine (189 mg, 1.07 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 77−78 °C (hexane/CH_2Cl_2); IR ν_{max}: 3385, 3021, 1746, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.40−7.27 (m, 7H), 6.92−6.85 (m, 2H), 5.19 (s, 2H), 4.76 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 156.9, 135.5, 133.5, 130.3, 128.6, 128.4, 128.2, 120.4, 111.1, 110.5, 87.1, 84.4, 67.6, 64.9, 55.6; ESI-HRMS calcd for $C_{18}H_{18}NO_4$ ($M + H^+$) 312.1230. Found 312.1223.

*Benzyl(3-(3-methoxylphenyl)-2-propynyl)oxycarbamate (**1i**).* According to **step 2**, *O*-(3-(3-methoxyphenyl)-2-propynyl)hydroxylamine (976 mg, 78% in 2 steps) was obtained from 3-bromo-1-(3-methoxyphenyl)-1-propyne[21] (1.59 g, 7.06 mmol) Eluent: hexane/Et_2O = 3/2. Colorless oil; IR ν_{max}: 3528, 3017, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.00−6.99 (m, 1H), 6.88 (dd, J = 8.1, 1.8 Hz, 1H), 5.64 (br s, 2H), 4.52 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 129.3, 124.3, 123.4, 116.6, 115.1, 86.2, 84.5, 64.1, 55.2; CI-HRMS calcd for $C_{10}H_{12}NO_2$ ($M+H^+$) 178.0868. Found 178.0869. According to **step 3**, **1i** (344 mg, 87%) was obtained from *O*-(3-(3-methoxyphenyl)-2-propynyl)hydroxylamine (223 mg, 1.26 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 62−63 °C (hexane); IR ν_{max}: 3539, 3386, 3023, 1748, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.37−7.32 (m, 5H), 7.21 (t, J = 7.8 Hz, 1H), 7.03 (dt, J = 7.8, 1.2 Hz, 1H), 6.98−6.96 (m, 1H), 6.89 (ddd, J = 7.8, 2.7, 1.2 Hz, 1H), 5.20 (s, 2H), 4.71 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 157.0, 135.4, 129.4, 128.6, 128.5, 128.3, 124.4, 123.0, 116.6, 115.4, 87.6, 82.8, 67.7, 64.8, 55.2,; ESI-HRMS calcd for $C_{18}H_{18}NO_4$ ($M + H^+$) 312.1230. Found 312.1232.

*Benzyl(3-(4-methoxylphenyl)-2-propynyl)oxycarbamate (**1j**).* According to **step 1**, 3-bromo-1-(4-methoxylphenyl)-1-propyne[23] (738 mg, 88%) was obtained from 3-(4-methoxylphenyl)-2-propyn-1-ol[20] (600 mg, 3.70 mmol). Eluent: hexane/Et_2O = 19/1. Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (dt, J = 9.0, 2.1 Hz, 2H), 6.84 (dt, J = 9.0, 2.1 Hz, 2H), 4.17 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 133.4, 114.2, 113.9, 86.7, 82.9, 55.3, 15.8. According to **step 2**, *O*-(3-(4-methoxyphenyl)-2-propynyl)hydroxylamine (297 mg, 48% in 2 steps) was obtained from 3-bromo-1-(4-methoxyphenyl)-1-propyne (788 mg, 3.50 mmol). Eluent: hexane/Et_2O = 2/3. Colorless oil; IR ν_{max}: 3539, 3016, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 6.9 Hz, 2H), 6.83 (d, J = 6.9 Hz, 2H), 5.61 (br s, 2H), 4.51 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 133.3, 114.5, 113.9, 86.3, 83.2, 64.2, 55.2; EI-HRMS calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0790. Found 177.0804. According to **step 3**, **1j** (174 mg, 99%) was obtained from *O*-(3-(4-methoxyphenyl)-2-propynyl)hydroxylamine (100 mg, 0.564 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 63−64 °C (hexane/CH_2Cl_2); IR ν_{max}: 3590, 3384, 3022, 2222, 1747, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.38−7.32 (m, 7H), 6.82 (d, J = 9.0 Hz, 2H), 5.19 (s, 2H), 4.69 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 157.0, 135.4, 133.4, 128.54, 128.48, 128.40, 128.3, 126.9, 114.0, 113.9, 87.7, 81.7, 67.6, 64.9, 55.2; EI-HRMS calcd for $C_{18}H_{17}NO_4$ (M^+) 311.1158. Found 311.1168.

*Benzyl(3-(2-nitrophenyl)-2-propynyl)oxycarbamate (**1k**).* According to **step 1**, 3-bromo-1-(2-nitrophenyl)-1-propyne (1.97 g, 94%) was obtained from 3-(2-nitrophenyl)-2-propyn-1-ol (1.54 g, 8.69 mmol). Eluent: hexane/AcOEt = 9/1. Brown crystals; mp 199−200 °C (MeOH); IR ν_{max}: 3015, 2293, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.1, 1.2 Hz, 1H), 7.66−7.57 (m, 2H), 7.52−7.46 (m, 1H), 4.20 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 134.9, 132.9, 129.3, 124.6, 117.5, 91.7, 81.5, 14.4; CI-HRMS calcd for $C_9H_7BrNO_2$ ($M+H^+$) 239.9660. Found 239.9651. According to **step 2**, *O*-(3-(2-nitrophenyl)-2-propynyl)hydroxylamine (754 mg, 49% in 2 steps) was obtained from 3-bromo-1-(2-nitrophenyl)-1-propyne (1.92 g, 7.98 mmol). Eluent: hexane/AcOEt = 13/7. Yellow crystals; mp 41−42 °C (hexane/Et_2O); IR ν_{max}: 3570, 3330, 1609, 1573, 1347 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.1, 1.2 Hz, 1H), 7.67−7.56 (m, 2H), 7.51−7.45 (m, 1H), 4.74 (br s, 2H), 4.58 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 134.6, 132.8, 128.8, 124.6, 117.9, 93.3, 81.6, 63.9; CI-HRMS calcd for $C_9H_9N_2O_3$ ($M + H^+$) 193.0613. Found 193.0607. According to **step 3**, **1k** (200 mg, 79%) was obtained from *O*-(3-(2-nitrophenyl)-2-propynyl)hydroxylamine (149 mg, 0.775 mmol). Eluent: hexane/AcOEt = 7/3. Pale brown crystals; mp 75−76 °C (hexane/CH_2Cl_2); IR ν_{max}: 3580, 3381, 3024, 1746, 1609, 1529, 1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.1, 0.9 Hz, 1H), 7.87 (br s, 1H), 7.63−7.54 (m, 2H), 7.51−7.45 (m, 1H), 7.40−7.29 (m, 5H), 5.21 (s, 2H), 4.77 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 149.6, 135.4, 134.7, 133.0, 129.1, 128.5, 128.4, 128.3, 124.7, 117.6, 91.4, 83.0, 67.6, 64.6; ESI-HRMS calcd for $C_{17}H_{15}N_2O_5$ ($M + H^+$) 327.0981. Found 327.0975.

*Benzyl(3-(3-nitrophenyl)-2-propynyl)oxycarbamate (**1l**).* According to **step 1**, 3-bromo-1-(3-nitrophenyl)-1-propyne (1.77 g, 97%) was obtained from 3-(3-nitrophenyl)-2-propyn-1-ol[24] (1.34 g, 7.55 mmol). Eluent: hexane/AcOEt = 9/1. Yellow crystals; mp 62−63 °C (MeOH/H_2O); IR ν_{max}: 3025, 1574, 1532, 1352, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (t, J = 1.5 Hz, 1H), 8.19 (ddd, J = 7.8, 2.1, 1.2 Hz, 1H), 7.74 (dt, J = 7.8, 1,5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 4.16 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 137.5, 129.4, 126.7, 123.9, 123.5, 86.8, 83.9, 14.1; EI-HRMS calcd for $C_9H_6BrNO_2$ (M^+) 238.9582. Found 238.9570. According to **step 2**, *O*-(3-(3-nitrophenyl)-2-propynyl)hydroxylamine (919 mg, 67% in 2 steps) was obtained from 3-bromo-1-(3-nitrophenyl)-1-propyne (1.70 g, 7.09 mmol). Eluent: hexane/AcOEt = 13/7. Pale yellow crystals; mp 37−38 °C (hexane/Et_2O); IR ν_{max}: 3571, 3331, 3014, 1531, 1351 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (t, J = 1.8 Hz, 1H), 8.17 (ddd, J = 7.8, 2.4, 1.2 Hz, 1H), 7.76 (dt, J = 7.8, 1.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 5.40 (br s, 2H), 4.55 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 137.4, 129.3, 126.6, 124.3, 123.2, 87.3, 83.6, 63.7;

EI-HRMS calcd for $C_9H_8N_2O_3$ (M^+) 192.0535. Found 192.0536. According to **step 3**, **1l** (280 mg, 90%) was obtained from *O*-(3-(3-nitrophenyl)-2-propynyl)hydroxylamine (183 mg, 0.952 mmol). Eluent: hexane/Et_2O = 1/1. Colorless crystals; mp 95−96 °C (hexane/CH_2Cl_2); IR ν_{max}: 3591, 3025, 1750, 1532, 1351 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (t, J = 1.5 Hz, 1H), 8.17 (dd, J = 8.4, 1.5 Hz, 1H), 7.77 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.37−7.32 (m, 5H), 5.21 (s, 2H), 4.74 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 148.0, 137.4, 135.3, 129.4, 128.6, 128.5, 128.3, 126.6, 123.9, 123.4, 85.9, 85.0, 67.8, 64.4; ESI-HRMS calcd for $C_{17}H_{15}N_2O_5$ ($M + H^+$) 327.0981. Found 327.0983.

Benzyl(3-(4-nitrophenyl)-2-propynyl)oxycarbamate (***1m***). According to **step 1**, 3-bromo-1-(4-nitrophenyl)-1-propyne (1.36 g, 91%) was obtained from 3-(4-nitrophenyl)-2-propyn-1-ol[25] (1.10 g, 6.20 mmol). Eluent: hexane/AcOEt = 9/1. Yellow crystals; mp 70−71 °C (MeOH/H_2O); IR ν_{max}: 3024, 1593 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 4.17 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 132.6, 128.9, 123.6, 89.3, 84.3, 14.0; EI-HRMS calcd for $C_9H_6BrNO_2$ (M^+) 238.9582. Found 238.9592. According to **step 2**, *O*-(3-(4-nitrophenyl)-2-propynyl)hydroxylamine (762 mg, 79% in 2 steps) was obtained from 3-bromo-1-(4-nitrophenyl)-1-propyne (1.20 g, 4.99 mmol). Eluent: hexane/AcOEt = 3/2. Colorless crystals; mp 104−105 °C (hexane/AcOEt); IR ν_{max}: 3570, 3332, 3019, 1594, 1520, 1344 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 5.71 (s, 2H), 4.55 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 132.5, 129.4, 123.5, 90.5, 84.2, 63.8; EI-HRMS calcd for $C_9H_8N_2O_3$ (M^+) 192.0535. Found 192.0534. According to **step 3**, **1m** (207 mg, 82%) was obtained from *O*-(3-(4-nitrophenyl)-2-propynyl)hydroxylamine (150 mg, 0.780 mmol). Eluent: hexane/Et_2O = 1/1. Colorless crystals; mp 114−115 °C (hexane/CH_2Cl_2); IR ν_{max}: 3594, 3381, 3030, 1749, 1595, 1520, 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 9.0 Hz, 2H), 7.74 (br s, 1H), 7.55 (d, J = 9.0 Hz, 2H), 7.38−7.33 (m, 5H), 5.21 (s, 2H), 4.75 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 147.4, 135.3, 132.5, 128.9, 128.6, 128.5, 128.3, 123.5, 88.4, 85.5, 67.8, 64.6; CI-HRMS calcd for $C_{17}H_{15}N_2O_5$ ($M + H^+$) 327.0981. Found 327.0977.

Benzyl(3-(1-naphthyl)-2-propynyl)oxycarbamate (***1n***). According to **step 2**, *O*-(3-(1-naphthyl)-2-propynyl)hydroxylamine (1.02 g, 72% in 2 steps) was obtained from 3-bromo-1-(1-naphthyl)-1-propyne[19] (1.76 g, 7.17 mmol). Eluent: hexane/Et_2O = 1/1. Pale yellow oil; IR ν_{max}: 3673, 3017, 2226, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 8.1 Hz, 1H), 7.81 (dd, J = 8.1, 3.9 Hz, 2H), 7.69 (dd, J = 7.2, 1.2 Hz, 1H), 7.58−7.46 (m, 2H), 7.42−7.37 (m, 1H), 5.68 (s, 2H), 4.66 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.3, 133.0, 130.7, 129.0, 128.2, 126.8, 126.4, 126.0, 125.1, 120.1, 89.7, 84.3, 64.2; EI-HRMS calcd for $C_{13}H_{11}NO$ (M^+) 197.0841. Found 197.0858. According to **step 3**, **1n** (257 mg, 95%) was obtained from *O*-(3-(1-naphthyl)-2-propynyl)hydroxylamine (160 mg, 0.811 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 64−65 °C (hexane); IR ν_{max}: 3507, 3382, 3012, 2227, 1747, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (dt, J = 7.8, 0.9 Hz, 1H), 7.83 (dd, J = 7.2, 1.2 Hz, 2H), 7.74 (br s, 1H), 7.67 (dd, J = 7.2, 1.2 Hz, 1H), 7.58−7.48 (m, 2H), 7.43−7.29 (m, 6H), 5.21 (s, 2H), 4.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 135.4, 133.3, 133.1, 131.0, 129.3, 128.6, 128.4, 128.29, 128.27, 126.9, 126.5, 126.0, 125.1, 119.7, 87.8, 85.8, 67.7, 65.0; EI-HRMS calcd for $C_{21}H_{17}NO_3$ (M^+) 331.1208. Found 331.1225.

Benzyl(3-(2-thienyl)-2-propynyl)oxycarbamate (***1o***). According to **step 1**, 3-bromo-1-(2-thienyl)-1-propyne (1.70 g, 96%) was obtained from 3-(2-thienyl)-2-propyn-1-ol[26] (1.20 g, 8.68 mmol). Eluent: hexane. Brown oil; IR ν_{max}: 3018, 2226 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, J = 5.1, 0.9 Hz, 1H), 7.24 (dd, J = 3.9, 0.9 Hz, 1H), 6.97 (dd, J = 5.1, 3.9 Hz, 1H), 4.17 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 128.0, 127.0, 122.0, 88.1, 80.1, 15.3; EI-HRMS calcd for C_7H_5BrS (M^+) 199.9295. Found 199.9306. According to **step 2**, *O*-(3-(2-thienyl)-2-propynyl)hydroxylamine (751 mg, 61% in 2 steps) was obtained from 3-bromo-1-(1-naphthyl)-1-propyne (1.61 g, 8.02 mmol. Eluent: hexane/Et_2O = 1/1. Yellow oil; IR ν_{max}: 3571, 3331, 3017, 2223, 1581 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.23 (m, 2H), 6.97 (dd, J = 5.1, 3.9 Hz, 1H), 5.63 (br s, 2H), 4.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.6, 127.4, 126.9, 122.3, 88.8, 79.5, 64.1; EI-HRMS calcd for C_7H_7NOS (M^+) 153.0248. Found 153.0257. According to **step 3**, **1o** (225 mg, 81%) was obtained from *O*-(3-(2-thienyl)-2-propynyl)hydroxylamine (148 mg, 0.966 mmol). Eluent: hexane/Et_2O = 7/3. Colorless crystals; mp 82−83 °C (hexane/CH_2Cl_2); IR ν_{max}: 3680, 3384, 3022, 2225, 1747, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.38−7.33 (m, 5H), 7.28 (dd, J = 5.1, 1.2 Hz, 1H), 7.24 (dd, J = 3.6, 1.2 Hz, 1H), 6.97 (dd, J = 5.1, 3.6 Hz, 1H), 5.21 (s, 2H), 4.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 135.4, 133.0, 128.6, 128.4, 128.3, 127.9, 127.0, 121.9, 87.1, 80.9, 67.7, 64.8; EI-HRMS calcd for $C_{15}H_{13}NO_3S$ (M^+) 287.0616. Found 287.0601.

Benzyl(3-(1-cyclohexenyl)-2-propynyl)oxycarbamate (***1p***). According to **step 1**, 3-bromo-1-(1-cyclohexenyl)-1-propyne[27] (1.99 g, 73%) was obtained from 3-(1-cyclohexenyl)-2-propyn-1-ol[28] (1.86 g, 13.7 mmol). Eluent: hexane. The spectral data of this compound were identical with those of the literature.[27] Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (quint, J = 3.0 Hz, 1H), 4.07 (s, 2H), 2.13−2.08 (m, 4H), 1.66−1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 120.0, 88.8, 81.6, 28.8, 25.6, 22.1, 21.3, 15.9. According to **step 2**, *O*-(3-(1-cyclohexenyl)-2-propynyl)hydroxylamine (680 mg, 53% in 2 steps) was obtained from 3-bromo-1-(1-cyclohexenyl)-1-propyne (1.72 g, 8.54 mmol). Eluent: hexane/AcOEt = 4/1. Colorless oil; IR ν_{max}: 3684, 3331, 2936, 2220, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (quint, J = 3.0 Hz, 1H), 5.53 (br s, 2H), 4.41 (s, 2H), 2.15−2.08 (m, 4H), 1.65−1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 120.0, 81.7, 64.3, 63.0, 29.1, 25.6, 22.2, 21.4; ESI-HRMS calcd for $C_9H_{14}NO$ ($M + H^+$) 152.1075. Found 152.1069. According to **step 3**, **1p** (441 mg, quant) was obtained from *O*-(3-(1-cyclohexenyl)-2-propynyl)hydroxylamine (200 mg, 1.32 mmol). Eluent: hexane/AcOEt = 4/1. Colorless crystals; mp 49.5−51.5 °C (hexane/AcOEt); IR ν_{max}: 3671, 3386, 2936, 2223, 1748, 1629 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (br s, 1H), 7.39−7.35 (m, 5H), 6.15 (quint, J = 1.8 Hz, 1H), 5.19 (s, 2H), 4.61 (m, 2H), 2.12−2.08 (m, 4H), 1.64−1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 136.4, 135.5, 128.6, 128.5, 128.3, 119.8, 89.7, 80.2, 67.6, 64.9, 28.9, 25.6, 22.2, 21.3; ESI-HRMS calcd for $C_{17}H_{19}NNaO_3$ ($M + Na^+$) 308.1263. Found 308.1256.

Benzyl(2-heptyn-1-yl)oxycarbamate (***1q***). 1-Bromo-2-heptyne[29] (3.90 g, 89%) was prepared according to ref.[20] Colorless oil; bp 70 °C/12 mmHg; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (t, J = 2.4 Hz, 2H), 2.28−2.21 (m, 2H), 1.55−1.37 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.2, 75.2, 30.4, 21.9, 18.6, 15.7, 13.5. According to **step 2**, *O*-(2-heptyn-1-yl)hydroxylamine (727 mg, 81% in 2 steps) was obtained from 1-bromo-2-heptyne (1.23 g, 7.03 mmol). Eluent: hexane/Et_2O = 2/3. Pale yellow oil; IR ν_{max}: 3672, 3518, 3330, 2960, 2224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.51 (br s, 2H), 4.29 (t, J = 2.1 Hz, 2H), 2.27−2.21 (m, 2H), 1.56−1.37 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.3, 75.3, 63.9, 30.5, 21.8, 18.3, 13.4; ESI-HRMS calcd for $C_7H_{14}NO$ ($M + H^+$) 128.1075. Found 128.1068. According to **step 3**, **1q** (186 mg, 83%) was obtained from *O*-(2-heptyn-1-yl)hydroxylamine (109 mg, 0.860 mmol). Eluent: hexane/Et_2O = 4/1. Colorless oil; IR ν_{max}: 3684, 3387, 2935, 1748, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.38−7.33 (m, 5H), 5.18 (s, 2H), 4.72 (t, J = 2.4 Hz, 2H), 2.42−2.18 (m, 2H), 1.53−1.32 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 135.5, 128.5, 128.4, 128.2, 88.9, 73.9, 67.5, 64.6, 30.4, 21.8, 18.4, 13.5; ESI-HRMS calcd for $C_{15}H_{20}NO_3$ ($M + H^+$) 262.1443. Found 262.1441.

Benzyl(4-phenyl-3-butyn-2-yl)oxycarbamate (***1r***). According to **step 1**, 2-bromo-4-phenyl-3-butyne (2.30 g, quant) was obtained from 4-phenyl-3-bytyn-2-ol (1.50 g, 10.3 mmol). Eluent: hexane. Colorless oil; IR ν_{max}:

3017, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.41 (m, 2H), 7.31 (dd, J = 5.1, 2.1 Hz, 3H), 5.86 (q, J = 6.9 Hz, 1H), 2.00 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 128.7, 128.2, 122.1, 89.2, 31.9, 27.5; HR-EIMS calcd for $C_{10}H_9Br$ (M^+) 207.9888. Found 207.9880. According to **step 2**, *O*-(4-phenyl-3-butyn-2-yl)hydroxylamine (660 mg, 43% in 2 steps) was obtained from 2-bromo-4-phenyl-3-butyne (2.00 g, 9.57 mmol). Eluent: hexane/AcOEt = 3/1. Colorless oil; IR ν_{max}: 3670, 3331, 2997, 2233, 1582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.44 (m, 2H), 7.34−7.28 (m, 3H), 5.51 (br s, 2H), 4.60 (qd, J = 6.6, 1.2 Hz, 1H), 1.49 (dd, J = 6.6, 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 128.3, 128.2, 122.5, 88.6, 84.9, 71.2, 20.3; ESI-HRMS calcd for $C_{10}H_{12}NO$ ($M + H^+$) 162.0919. Found 162.0913. According to **step 3**, **1r** (445 mg, quant) was obtained from *O*-(4-phenyl-3-butyn-2-yl)hydroxylamine (200 mg, 1.24 mmol). Eluent: hexane/AcOEt = 5/1. Colorless crystals; mp 72−74 °C (hexane/AcOEt); IR ν_{max}: 3388, 3022, 2230, 1749, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.44−7.41 (m, 2H), 7.37−7.29 (m, 8H), 5.19 (d, J = 2.1 Hz, 2H), 4.88 (q, J = 6.9 Hz, 1H), 1.56 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 135.6, 131.8, 128.6, 128.4, 128.3, 128.2, 122.1, 87.2, 86.0, 72.3, 67.6; ESI-HRMS calcd for $C_{18}H_{18}NO_3$ ($M + H^+$) 296.1287. Found 296.1278; Anal. calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found C, 73.40; H, 5.72; N, 4.81.

Isopropyl(3-(2-methylphenyl)-2-propynyl)oxycarbamate (**1s**). According to **step 3**, **1s** (220 mg, 82%) was obtained from *O*-(3-(2-methylphenyl)-2-propynyl)hydroxylamine (175 mg, 1.08 mmol). Eluent: hexane/Et_2O = 7/3. Colorless oil; IR ν_{max}: 3549, 3385, 2968, 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.27−7.13 (m, 3H), 5.02 (sept, J = 6.3 Hz, 1H), 4.76 (s, 2H), 2.44 (s, 3H), 1.28 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 140.4, 132.2, 129.4, 128.7, 125.5, 121.9, 86.9, 86.4, 70.0, 64.7, 21.9, 20.6; CI-HRMS calcd for $C_{14}H_{18}NO_3$ ($M + H^+$) 248.1286. Found 248.1276.

Isopropyl(3-(4-methylphenyl)-2-propynyl)oxycarbamate (**1t**). According to **step 3**, **1t** (243 mg, 93%) was obtained from *O*-(3-(4-methylphenyl)-2-propynyl)hydroxylamine (168 mg, 1.04 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 73−74 °C (hexane); IR ν_{max}: 3687, 2928, 1743, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (br s, 1H), 7.35 (d, J = 7.8 Hz, 2H), 7.12, (d, J = 7.8 Hz, 2H), 5.02 (sept, J = 6.3 Hz, 1H), 4.70 (s, 2H), 2.35 (s, 3H), 1.28 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.9, 138.9, 131.7, 129.0, 119.0, 87.6, 82.5, 70.0, 64.7, 21.9, 21.4; CI-HRMS calcd for $C_{14}H_{18}NO_3$ ($M + H^+$) 248.1286. Found 248.1268.

Isopropyl(3-(2-methoxyphenyl)-2-propynyl)oxycarbamate (**1u**). According to **step 3**, **1u** (208 mg, 92%) was obtained from *O*-(3-(2-methoxylphenyl)-2-propynyl)hydroxylamine (152 mg, 0.857 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 82−83 °C (hexane/Et_2O); IR ν_{max}: 3386, 2985, 1742, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.41 (dd, J = 7.8, 1.8 Hz, 1H), 7.34−7.27 (m, 1H), 6.94−6.87 (m, 2H), 5.02 (sept, J = 6.3 Hz, 1H), 4.76 (s, 2H), 3.89 (s, 3H), 1.28 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 156.7, 133.5, 130.2, 120.4, 111.2, 110.5, 87.2, 84.1, 69.8, 64.7, 55.6, 21.9; EI-HRMS calcd for $C_{14}H_{17}NO_4$ (M^+) 263.1158. Found 263.1172.

Isopropyl(3-(3-methoxyphenyl)-2-propynyl)oxycarbamate (**1v**). According to **step 3**, **1v** (176 mg, 87%) was obtained from *O*-(3-(3-methoxylphenyl)-2-propynyl)hydroxylamine (135 mg, 0.761 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 43−44 °C (hexane); IR ν_{max}: 3674, 3385, 2986, 1743, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.21 (t, J = 8.4 Hz, 1H), 7.07−6.98 (m, 2H), 6.89 (ddd, J = 8.4, 2.1, 0.9 Hz, 1H), 5.01 (sept, J = 6.3 Hz, 1H), 4.71 (s, 2H), 3.78 (s, 3H), 1.27 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 157.0, 129.3, 124.3, 123.0, 116.6, 115.3, 87.2, 83.0, 69.9, 64.5, 55.1, 21.8; EI-HRMS calcd for $C_{14}H_{17}NO_4$ (M^+) 263.1158. Found 263.1141.

Isopropyl(3-(4-methoxyphenyl)-2-propynyl)oxycarbamate (**1w**). According to **step 3**, **1w** (148 mg, 98%) was obtained from *O*-(3-(3-methoxylphenyl)-2-propynyl)hydroxylamine (100 mg, 0.564 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 83−84 °C (hexane/AcOEt); IR ν_{max}: 3691, 2931, 1743, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (br s, 1H), 7.39 (dd, J = 6.6, 2.1 Hz, 2H), 6.83 (dd, J = 6.6, 2.1 Hz, 2H), 5.02 (sept, J = 6.3 Hz, 1H), 4.70 (s, 2H), 3.81 (s, 3H), 1.28 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 156.9, 133.4, 114.2, 113.9, 87.5, 81.8, 70.0, 64.8, 55.3, 21.9; CI-HRMS calcd for $C_{14}H_{18}NO_4$ ($M + H^+$) 264.1236. Found 264.1220.

Isopropyl(3-(2-nitrophenyl)-2-propynyl)oxycarbamate (**1x**). According to **step 3**, **1x** (315 mg, 79%) was obtained from *O*-(3-(2-nitrophenyl)-2-propynyl)hydroxylamine (275 mg, 1.43 mmol). Eluent: hexane/Et_2O = 7/3. Colorless crystals; mp 80−81 °C (hexane); IR ν_{max}: 3672, 3382, 3022, 1741, 1609, 1528, 1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J = 8.1, 1.2 Hz, 1H), 7.76 (s, 1H), 7.67−7.58 (m, 2H), 7.52−7.47 (m, 1H), 5.02 (sept, J = 6.3 Hz, 1H), 4.78 (s, 2H), 1.28 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 149.6, 134.7, 132.9, 129.1, 124.6, 117.6, 91.6, 82.8, 70.0, 64.4, 21.9; CI-HRMS calcd for $C_{13}H_{15}N_2O_5$ ($M + H^+$) 279.0981. Found: 279.0986.

Isopropyl(3-(3-nitrophenyl)-2-propynyl)oxycarbamate (**1y**). According to **step 3**, **1y** (329 mg, 74%) was obtained from *O*-(3-(3-nitrophenyl)-2-propynyl)hydroxylamine (307 mg, 1.60 mmol). Eluent: hexane/AcOEt = 7/3. Colorless crystals; mp 111−112 °C (hexane/Et_2O); IR ν_{max}: 3688, 3384, 3023, 1746, 1532, 1443, 1351 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (t, J = 1.5 Hz, 1H), 8.19 (ddd, J = 8.1, 2.4, 1.5 Hz, 1H), 7.76 (dt, J = 7.8, 1.5 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.50 (br s, 1H), 5.04 (sept, J = 6.3 Hz, 1H), 4.74 (s, 2H), 1.29 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 148.0, 137.4, 129.4, 126.6, 124.0, 123.4, 86.1, 84.8, 70.2, 64.4, 21.9; EI-HRMS calcd for $C_{13}H_{14}N_2O_5$ (M^+) 278.0903. Found 278.0911.

Isopropyl(3-(4-nitrophenyl)-2-propynyl)oxycarbamate (**1z**). According to **step 3**, **1z** (242 mg, 83%) was obtained from *O*-(3-(4-nitrophenyl)-2-propynyl)hydroxylamine (200 mg, 1.04 mmol). Eluent: hexane/AcOEt = 3/1. Colorless crystals; mp 100−101 °C (hexane/Et_2O); IR ν_{max}: 3691, 3383, 2928, 1745, 1596, 1521, 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 9.0 Hz, 2H), 7.61 (d, J = 9.0 Hz, 2H), 7.58 (s, 1H), 5.03 (sept, J = 6.3 Hz, 1H), 4.75 (s, 2H), 1.29 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 147.4, 132.5, 129.0, 123.5, 88.7, 85.3, 70.2, 64.5, 21.9; EI-HRMS calcd for $C_{13}H_{14}N_2O_5$ (M^+) 278.0903. Found 278.0920.

Isopropyl(3-(1-naphthyl)-2-propynyl)oxycarbamate (**1aa**). According to **step 3**, **1aa** (364 mg, 89%) was obtained from *O*-(3-(1-naphthyl)-2-propynyl)hydroxylamine (285 mg, 1.44 mmol). Eluent: hexane/Et_2O = 1/1. Colorless crystals; mp 67−68 °C (hexane/AcOEt); IR ν_{max}: 3688, 3385, 3021, 2228, 1741, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.69 (dd, J = 7.2, 1.2 Hz, 1H), 7.64 (s, 1H), 7.60−7.49 (m, 2H), 7.44−7.39 (m, 1H), 5.03 (sept, J = 6.3 Hz, 1H), 4.87 (s, 2H), 1.28 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 133.3, 133.0, 130.9, 129.2, 128.3, 126.9, 126.5, 126.0, 125.1, 119.8, 88.0, 85.6, 70.1, 64.8, 21.9; EI-HRMS calcd for $C_{17}H_{17}NO_3$ (M^+) 283.1208. Found 283.1223.

Isopropyl(3-(2-thienyl)-2-propynyl)oxycarbamate (**1ab**). According to **step 3**, **1ab** (311 mg, 97%) was obtained from *O*-(3-(2-thienyl)-2-propynyl)hydroxylamine (205 mg, 1.33 mmol). Eluent: hexane/Et_2O = 3/2. Colorless crystals; mp 32−33 °C (hexane); IR ν_{max}: 3676, 3384, 2986, 2226, 1742, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.28 (dd, J = 5.1, 1.2 Hz, 1H), 7.25 (dd, J = 3.6, 1.2 Hz, 1H), 6.97 (dd, J = 5.1, 3.6 Hz, 1H), 5.02 (sept, J = 6.3 Hz, 1H), 4.72 (s, 2H), 1.28 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 132.9, 127.8, 127.0, 122.0, 87.3, 80.8, 70.1, 64.7, 21.9; EI-HRMS calcd for $C_{11}H_{13}NO_3S$ (M^+) 239.0616. Found 239.0630.

Isopropyl(3-(1-cyclohexenyl)-2-propynyl)oxycarbamate (**1ac**). According to **step 3**, **1ac** (441 mg, quant) was obtained from *O*-(3-(1-cyclohexenyl)-2-propynyl)hydroxylamine (180 mg, 1.19 mmol). Eluent: hexane/AcOEt = 4/1. Colorless oil; IR ν_{max}: 3386, 2939, 2223, 1743, 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (br s, 1H), 6.16 (quint,

J = 2.1 Hz, 1H), 5.01 (sept, J = 6.3 Hz, 1H), 4.60 (s, 2H), 2.12−2.09 (m, 4H), 1.65−1.57 (m, 4H), 1.28 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 136.3, 119.9, 89.5, 80.4, 69.9, 64.8, 29.0, 25.6, 22.2, 21.9, 21.4; ESI-HRMS calcd for $C_{13}H_{20}NO_3$ (M + H^+) 238.1443. Found 238.1436.

*Isopropyl(2-heptyn-1-yl)oxycarbamate (**1ad**).* According to **step 3**, **1ad** (290 mg, 87%) was obtained from *O*-(2-heptyn-1-yl)hydroxylamine (198 mg, 1.56 mmol). Eluent: hexane/Et_2O = 4/1. Colorless oil; IR ν_{max}: 3677, 3386, 2936, 1743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 5.01 (sept, J = 6.3 Hz, 1H), 4.47 (t, J = 2.4 Hz, 2H), 2.26−2.20 (m, 2H), 1.53−1.37 (m, 4H), 1.28 (d, J = 6.3 Hz, 6H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 88.7, 74.0, 69.8, 64.4, 30.4, 21.9, 21.8, 18.3, 13.4; ESI-HRMS calcd for $C_{11}H_{20}NO_3$ (M + H^+) 214.1443. Found 214.1433.

*Isopropyl(4-phenyl-3-butyn-2-yl)oxycarbamate (**1ae**).* According to **step 3**, **1ae** (274 mg, 89%) was obtained from *O*-(4-phenyl-3-butyn-2-yl)hydroxylamine (200 mg, 1.24 mmol). Eluent: hexane/AcOEt = 4/1. Colorless crystals; mp 61−62 °C (hexane/AcOEt); IR ν_{max}: 3692, 2988, 2230, 2744, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (br s, 1H), 7.47−7.43 (m, 2H), 7.31 (dd, J = 5.1, 2.1 Hz, 3H), 5.00 (sept, J = 6.3 Hz, 1H), 4.87 (q, J = 6.6 Hz, 1H), 1.57 (d, J = 6.6 Hz, 3H), 1.27 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 131.8, 128.6, 128.2, 122.2, 87.4, 85.8, 72.1, 69.8, 21.92, 21.88, 19.9; ESI-HRMS calcd for $C_{14}H_{18}NO_3$ (M + H^+) 248.1287. Found 248.1277; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found C, 68.06; H, 6.85; N, 5.63.

General Procedure for the Preparation of 2,5-Dihydroisoxazole 2. To a solution of **1** (1 equiv) in dry CH_2Cl_2 (0.1 M) was added $I(coll)_2PF_6$ (1.5−2 equiv) at rt and the reaction mixture was stirred for 20−30 min. The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give **2**.

*Benzyl 2,5-Dihydro-4-iodo-3-phenyl-2H-isoxazole-2-carboxylate (**2a**).* **2a** (114 mg, 97%) was obtained from **1a** (80.0 mg, 0.284 mmol). Eluent: hexane/Et_2O = 5/2. Yellow amorphous solid; IR ν_{max}: 2926, 1729, 1561 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.53 (m, 2H), 7.38−7.36 (m, 3H), 7.24−7.21 (m, 3H), 6.97−6.94 (m, 2H), 5.05 (s, 2H), 4.99 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 141.0, 134.7, 129.9, 129.3, 128.7, 128.3, 128.1, 127.7, 81.4, 68.3, 67.5; EI-HRMS calcd for $C_{17}H_{14}INO_3$ (M^+) 407.0018. Found 407.0026.

*Benzyl 2,5-Dihydro-4-iodo-3-(2-methylphenyl)-2H-isoxazole-2-carboxylate (**2f**).* **2f** (120 mg, 93%) was obtained from **1f** (90.0 mg, 0.304 mmol). Eluent: hexane/Et_2O = 7/3. Brown oil; IR ν_{max}: 3023, 1722, 1563 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.14 (m, 7H), 6.96−6.93 (m, 2H), 5.04 (s, 2H), 5.00 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 141.0, 137.2, 134.7, 130.2, 129.8, 129.5, 129.4, 128.3, 128.1, 127.9, 125.5, 80.3, 68.1, 67.4, 19.6; ESI-HRMS calcd for $C_{18}H_{17}INO_3$ (M + H^+) 422.0253. Found 422.0242.

*Benzyl 2,5-Dihydro-4-iodo-3-(4-methylphenyl)-2H-isoxazole-2-carboxylate (**2g**).* **2g** (57.0 mg, 89%) was obtained from **1g** (45.0 mg, 0.152 mmol). Eluent: hexane/Et_2O = 7/3. Pale yellow crystals; mp 61−62 °C (hexane/CH_2Cl_2); IR ν_{max}: 3018, 1727, 1637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J = 6.6, 1.5 Hz, 2H), 7.26−7.16 (m, 5H), 7.00−6.96 (m, 2H), 5.06 (s, 2H), 4.98 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 141.1, 139.4, 134.8, 128.9, 128.7, 128.2, 128.1, 127.8, 127.0, 81.4, 68.4, 66.7, 21.5; EI-HRMS calcd for $C_{18}H_{16}INO_3$ (M^+) 421.0175. Found 421.0160.

*Benzyl 2,5-Dihydro-4-iodo-3-(2-methoxylphenyl)-2H-isoxazole-2-carboxylate (**2h**).* **2h** (124 mg, 95%) was obtained from **1h** (92.2 mg, 0.296 mmol). Eluent: hexane/Et_2O = 3/2. Yellow amorphous solid; IR ν_{max}; 3018, 1720, 1596 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 6.99−6.94 (m, 3H), 6.08 (d, J = 8.1 Hz, 1H), 5.04 (s, 2H), 5.02 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 152.2, 138.6, 135.0, 130.90, 130.86, 128.3, 128.0, 127.9, 120.1, 118.9, 111.1, 80.5, 67.9, 67.5, 55.4; ESI-HRMS calcd for $C_{18}H_{17}INO_4$ (M + H^+) 438.0202. Found 438.0187.

*Benzyl 2,5-Dihydro-4-iodo-3-(3-methoxylphenyl)-2H-isoxazole-2-carboxylate (**2i**).* **2i** (138 mg, 98%) was obtained from **1i** (100 mg, 0.321 mmol). Eluent: hexane/Et_2O = 7/3. Pale yellow crystals; mp 79−80 °C (hexane/CH_2Cl_2); IR ν_{max}: 3022, 1730, 1597 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.20 (m, 4H), 7.15 (dt, J = 7.5, 1.5 Hz, 1H), 7.07 (dd, J = 8.1, 1.5 Hz, 1H), 7.00−6.97 (m, 2H), 6.93 (ddd, J = 8.1, 2.7, 1.5 Hz, 1H), 5.07 (s, 2H), 4.99 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 154.6, 141.0, 134.7, 131.1, 129.2, 128.3, 128.2, 127.8, 121.2, 115.4, 113.9, 81.5, 68.4, 67.9, 55.2; ESI-HRMS calcd for $C_{18}H_{17}INO_4$ (M + H^+) 438.0202. Found 438.0202.

*Benzyl 2,5-Dihydro-4-iodo-3-(4-methoxylphenyl)-2H-isoxazole-2-carboxylate (**2j**).* **2j** (99.1 mg, 80%) was obtained from **1j** (89.0 mg, 0.285 mmol). Eluent: hexane/Et_2O = 7/3. Colorless crystals; mp 98−99 °C (hexane/CH_2Cl_2); IR ν_{max}: 3021, 1727, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.7 Hz, 2H), 7.25−7.21 (m, 3H), 7.02−6.99 (m, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.07 (s, 2H), 4.96 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 154.7, 140.8, 134.8, 130.2, 128.3, 128.1, 127.8, 122.1, 113.5, 81.3, 68.3, 66.0, 55.2; EI-HRMS Calcd for $C_{18}H_{16}INO_4$ (M^+) 437.0124. Found 437.0111.

*Benzyl 2,5-Dihydro-4-iodo-3-(2-nitrophenyl)-2H-isoxazole-2-carboxylate (**2k**).* **2k** (95.0 mg, 75%) was obtained from **1k** (91.4 mg, 0.280 mmol). Eluent: hexane/Et_2O = 3/2. Brown amorphous solid; IR ν_{max}; 3024, 1723, 1608, 1531, 1349 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.1, 1.2 Hz, 1H), 7.63 (td, J = 7.5, 1.5 Hz, 1H), 7.53−7.41 (m, 2H), 7.28−7.23 (m, 3H), 7.06−7.03 (m, 2H), 5.10 (br d, J = 10.5 Hz, 2H), 4.98 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 147.8, 138.2, 134.4, 133.4, 132.0, 130.4, 128.4, 128.3, 125.7, 124.8, 80.7, 68.5, 66.3; ESI-HRMS calcd for $C_{17}H_{14}IN_2O_5$ (M + H^+) 452.9942. Found 452.9952.

*Benzyl 2,5-Dihydro-4-iodo-3-(3-nitrophenyl)-2H-isoxazole-2-carboxylate (**2l**).* **2l** (106 mg, 81%) was obtained from **1l** (94.2 mg, 0.288 mmol). Eluent: hexane/Et_2O = 13/7. Yellow crystals; mp 75−76 °C (hexane/CH_2Cl_2); IR ν_{max}; 3025, 1734, 1612, 1532, 1348 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (t, J = 1.8 Hz, 1H), 8.18−8.15 (m, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.29−7.22 (m, 3H), 7.05 (dd, J = 7.5, 1.8 Hz, 2H), 5.05 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 147.9, 139.2, 134.5, 134.2, 131.7, 129.1, 128.6, 128.5, 128.2, 123.9, 123.8, 81.7, 70.2, 68.9; ESI-HRMS calcd for $C_{17}H_{14}IN_2O_5$ (M + H^+) 452.9942. Found 452.9954.

*Benzyl 2,5-Dihydro-4-iodo-3-(4-nitrophenyl)-2H-isoxazole-2-carboxylate (**2m**).* **2m** (72.6 mg, 87%) was obtained from **1m** (60.2 mg, 0.184 mmol). Eluent: hexane/Et_2O = 13/7. Yellow crystals; mp 111−113 °C (hexane/CH_2Cl_2); IR ν_{max}: 3026, 1735, 1599, 1523, 1346 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.28−7.21 (m, 3H), 7.04 (br d, J = 6.3 Hz, 2H), 5.05 (s, 2H), 5.04 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 147.8, 139.5, 136.3, 134.2, 129.6, 128.7, 128.4, 128.3, 123.4, 81.9, 70.9, 69.0; EI-HRMS calcd for $C_{17}H_{13}IN_2O_5$ (M^+) 451.9869. Found 451.9881.

*Benzyl 2,5-Dihydro-4-iodo-3-(1-naphthyl)-2H-isoxazole-2-carboxylate (**2n**).* **2n** (134 mg, 95%) was obtained from **1n** (102 mg, 0.307 mmol). Eluent: hexane/Et_2O = 7/3. Yellow amorphous solid; IR ν_{max}: 3020, 1724, 1596 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93−7.90 (m, 1H), 7.86−7.82 (m, 2H), 7.51−7.40 (m, 4H), 7.19−7.05 (m, 3H), 6.62 (d, J = 7.2 Hz, 2H), 5.16 (d, J = 4.2 Hz, 2H), 4.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 140.2, 134.4, 133.4, 131.1, 129.9, 128.4, 128.1, 128.0, 127.7, 127.5, 126.7, 126.2, 125.1, 124.9, 80.8, 68.9, 68.2; EI-HRMS calcd for $C_{21}H_{16}INO_3$ (M^+) 457.0175. Found 457.0195.

*Benzyl 2,5-Dihydro-4-iodo-3-(2-thienyl)-2H-isoxazole-2-carboxylate (**2o**).* **2o** (124 mg, 96%) was obtained from **1o** (90.1 mg, 0.313 mmol). Eluent: hexane/Et_2O = 4/1. Yellow amorphous solid; IR ν_{max}:

3028, 1733, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, J = 3.6, 1.2 Hz, 1H), 7.41 (dd, J = 4.8, 1.2 Hz, 1H), 7.29−7.27 (m, 3H), 7.14−7.11 (m, 2H), 7.06 (dd, J = 4.8, 3.6 Hz, 1H), 5.15 (s, 2H), 4.93 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 137.4, 134.8, 129.8, 128.4, 128.3, 127.9, 127.6, 126.8, 81.6, 69.0, 68.7; EI-HRMS calcd for $C_{15}H_{12}INO_3S$ (M^+) 412.9583. Found 412.9572.

*Benzyl 2,5-Dihydro-4-iodo-3-(1-cyclohexenyl)-2H-isoxazole-2-carboxylate (**2p**).* **2p** (25.5 mg, 80%) was obtained from **1p** (22.0 mg, 0.0771 mmol). Eluent: hexane/AcOEt = 4/1. Colorless oil; IR ν_{max}: 2973, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.33 (m, 5H), 6.01 (quint, J = 2.1 Hz, 1H), 5.18 (s, 2H), 4.85 (s, 2H), 2.10−2.09 (m, 4H), 1.55−1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 142.7, 135.1, 132.4, 128.53, 128.49, 128.2, 80.5, 68.5, 64.5, 26.9, 25.2, 22.1, 21.6; ESI-HRMS calcd for $C_{17}H_{19}INO_3$ ($M + H^+$) 412.0410. Found 412.0404.

*Benzyl 3-Butyl-2,5-dihydro-4-iodo-2H-isoxazole-2-carboxylate (**2q**).* **2q** (28.5 mg, 94%) was obtained from **1q** (20.4 mg, 0.0781 mmol). Eluent: hexane/AcOEt = 4/1. Colorless oil; IR ν_{max}: 2962, 1713, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.31 (m, 5H), 5.23 (s, 2H), 4.82 (t, J = 1.2 Hz, 2H), 2.63 (tt, J = 7.5, 1.2 Hz, 2H), 1.55−1.45 (m, 2H), 1.37−1.25 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 141.5, 135.2, 128.6, 128.50, 128.46, 79.2, 68.1, 63.7, 29.4, 28.0, 22.2, 13.8; ESI-HRMS calcd for $C_{15}H_{19}INO_3$ ($M + H^+$) 388.0410. Found 388.0405.

*Benzyl 2,5-Dihydro-4-iodo-3-phenyl-5-methyl-2H-isoxazole-2-carboxylate (**2r**).* **2r** (38.2 mg, 96%) was obtained from **1r** (28.0 mg, 0.0948 mmol). Eluent: hexane/AcOEt = 3/1. This product was unstable under concentrated condition and gradually decomposed so that the selected data of **2r** were shown as below. Brown oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5H), 7.26−7.19 (m, 3H), 6.98−6.94 (m, 2H), 5.23 (q, J = 6.3 Hz, 1H), 5.06 (s, 2H), 1.50 (d, J = 6.3 Hz, 3H).

General Procedure for the Preparation of Isoxazole 3. To a solution of **1** (1 equiv) in dry CH_2Cl_2 (0.1 M) was added NIS (2.5 equiv) followed by $BF_3 \cdot OEt_2$ (2.5 equiv) at 0 °C and the reaction mixture was stirred for 15−45 min. The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give **3**.

*4-Iodo-3-phenylisoxazole (**3a**).* **3a** (36.8 mg, 63%) was obtained from **1c** (50.0 mg, 0.214 mmol). Eluent: hexane/Et_2O = 19/1. Colorless crystals; mp 92−93 °C (hexane); IR ν_{max}: 3018, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.83−7.80 (m, 2H), 7.51−7.48 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 162.1, 130.2, 128.6, 127.8, 58.0; EI-HRMS calcd for C_9H_6INO (M^+) 270.9494. Found 270.9506.

*4-Iodo-3-(2-methylphenyl)isoxazole (**3s**).* **3s** (49.0 mg, 71%) was obtained from **1s** (59.2 mg, 0.239 mmol). Eluent: hexane/Et_2O = 19/1. Colorless crystals; mp 53−54 °C (hexane); IR ν_{max}: 3019, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.42−7.29 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 161.6, 137.4, 130.5, 130.0, 129.9, 127.3, 125.7, 61.2, 20.0; EI-HRMS calcd for $C_{10}H_8INO$ (M^+) 284.9651. Found 284.9674.

*4-Iodo-3-(4-methylphenyl)isoxazole (**3t**).* **3t** (68.7 mg, 59%) was obtained from **1t** (101 mg, 0.407 mmol). Eluent: hexane/Et_2O = 19/1. Colorless crystals; mp 57−58 °C (hexane); IR ν_{max}: 3017, 2928, 1614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 162.0, 140.3, 129.3, 128.4, 124.9, 58.1, 21.4; EI-HRMS calcd for $C_{10}H_8INO$ (M^+) 284.9651. Found 284.9651.

*4-Iodo-3-(2-methoxylphenyl)isoxazole (**3u**).* **3u** (59.7 mg, 80%) was obtained from **1u** (65.1 mg, 0.247 mmol). Eluent: hexane/Et_2O = 17/3. Pale yellow crystals; mp 60−61 °C (hexane/Et_2O); IR ν_{max}: 3017, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.51−7.45 (m, 1H), 7.36 (dd, J = 7.5, 1.8 Hz, 1H), 7.08−6.99 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 161.4, 157.2, 131.7, 131.2, 120.6, 116.8, 111.1, 61.5, 55.3; EI-HRMS calcd for $C_{10}H_8INO_2$ (M^+) 300.9600. Found: 300.9616.

*4-Iodo-3-(3-methoxylphenyl)isoxazole (**3v**).* **3v** (45.5 mg, 58%) was obtained from **1v** (68.0 mg, 0.258 mmol). Eluent: hexane/Et_2O = 9/1. Colorless crystals; mp 54−55 °C (hexane); IR ν_{max}: 3018, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.42−7.40 (m, 2H), 7.35 (d, J = 1.8 Hz, 1H), 7.06−7.02 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 161.9, 159.6, 129.7, 128.9, 120.9, 116.3, 113.6, 58.0, 55.3; EI-HRMS calcd for $C_{10}H_8INO_2$ (M^+) 300.9600. Found 300.9621.

*4-Iodo-3-(4-methoxylphenyl)isoxazole (**3w**).* **3w** (80.9 mg, 70%) was obtained from **1w** (100 mg, 0.379 mmol). Eluent: hexane/Et_2O = 9/1. Colorless crystals; mp 64−65 °C (hexane); IR ν_{max}: 3018, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 161.6, 161.1, 129.9, 120.1, 114.0, 58.0, 55.3; EI-HRMS calcd for $C_{10}H_8INO_2$ (M^+) 300.9600. Found 300.9613.

*4-Iodo-3-(2-nitrophenyl)isoxazole (**3x**).* **3x** (49.0 mg, 50%) was obtained from **1x** (86.1 mg, 0.309 mmol). Eluent: hexane/Et_2O = 3/2. Yellow crystals; mp 108−109 °C (hexane/Et_2O); IR ν_{max}: 3014, 1576, 1533, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.25 (dd, J = 8.1, 1.5 Hz, 1H), 7.81−7.70 (m, 2H), 7.53 (dd, J = 7.2, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 161.6, 148.2, 133.6, 132.5, 131.3, 125.1, 123.6, 60.3; EI-HRMS calcd for $C_9H_5IN_2O_3$ (M^+) 315.9345. Found 315.9366.

*4-Iodo-3-(3-nitrophenyl)isoxazole (**3y**).* **3y** (73.0 mg, 70%) was obtained from **1y** (90.8 mg, 0.326 mmol). Eluent: hexane/Et_2O = 17/3. Pale yellow crystals; mp 131−132 °C (hexane); IR ν_{max}: 3022, 1606, 1534, 1352 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (t, J = 1.8 Hz, 1H), 8.55 (s, 1H), 8.37 (ddd, J = 8.1, 2.4, 1.2 Hz, 1H), 8.19 (ddd, J = 8.1, 1.5, 1.2 Hz, 1H), 7.71 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 160.3, 148.2, 134.3, 129.8, 129.6, 124.9, 123.6, 57.4; EI-HRMS calcd for $C_9H_5IN_2O_3$ (M^+) 315.9345. Found 315.9333.

*4-Iodo-3-(4-nitrophenyl)isoxazole (**3z**).* **3z** (71.9 mg, 62%) was obtained from **1z** (100 mg, 0.359 mmol). Eluent: hexane/Et_2O = 4/1. Pale yellow crystals; mp 172−173 °C (hexane/CH_2Cl_2); IR ν_{max}: 3024, 2927, 1605, 1526, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.37 (d, J = 9.0 Hz, 2H), 8.05 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 160.5, 148.9, 134.1, 129.6, 123.8, 57.4; EI-HRMS calcd for $C_9H_5IN_2O_3$ (M^+) 315.9345. Found 315.9357.

*4-Iodo-3-(1-naphthyl)isoxazole (**3aa**).* **3aa** (89.2 mg, 79%) was obtained from **1aa** (100 mg, 0.353 mmol). Eluent: hexane/Et_2O = 19/1. Colorless crystals; mp 101−102 °C (hexane); IR ν_{max}: 3017, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.01−7.90 (m, 2H), 7.78 (dd, J = 6.9, 2.1 Hz, 1H), 7.58−7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 161.9, 133.6, 131.3, 130.5, 128.6, 128.4, 126.9, 126.4, 125.6, 125.1, 124.9, 61.8; EI-HRMS calcd for $C_{13}H_8INO$ (M^+) 320.9651. Found 320.9664.

*4-Iodo-3-(2-thienyl)isoxazole (**3ab**).* **3ab** (58.5 mg, 45%) was obtained from **1ab** (108 mg, 0.451 mmol). Eluent: hexane/Et_2O = 19/1. Colorless crystals; mp 33−35 °C (hexane/CH_2Cl_2); IR ν_{max}: 3018, 1558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.91 (dd, J = 3.6, 1.2 Hz, 1H), 7.49 (dd, J = 5.1, 1.2 Hz, 1H), 7.18 (dd, J = 5.1, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 157.3, 129.0, 128.6, 128.5, 127.6, 56.9; EI-HRMS calcd for C_7H_4INOS (M^+) 276.9058. Found 276.9065.

*4-Iodo-3-(1-cyclohexenyl)isoxazole (**3ac**).* **3ac** (23.6 mg, 66%) was obtained from **1ac** (31.0 mg, 0.131 mmol). Eluent: hexane/AcOEt = 5/1. Colorless crystals; mp 62−63 °C (hexane/AcOEt); IR ν_{max}: 2934, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 6.67 (quint, J = 1.8 Hz, 1H), 2.45−2.44 (m, 2H), 2.29−2.23 (m, 2H), 1.81−1.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 161.8, 133.0, 126.8, 56.3, 26.7, 25.5, 22.3, 21.6; ESI-HRMS calcd for $C_9H_{11}INO$ ($M + H^+$) 275.9885. Found 275.9880.

*3-Butyl-4-iodoisoxazole (3ad) and 3-(1-Iodobutyl)-4-iodoisoxazole (**3ad′**).* **3ad** (26.4 mg, 53%) and **3ad′** (11.6 mg, 16%) were obtained as unseparatable mixture from **1ad** (42.0 mg, 0.197 mmol). Eluent: hexane/AcOEt = 5/1. Selected data of **3ad**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 2.66 (t, J = 7.5 Hz, 2H), 1.70 (quint, J = 7.5 Hz, 2H), 1.42 (sext, J = 7.5 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H); ESI-HRMS calcd for $C_7H_{11}INO$ ($M + H^+$) 251.9880. Found 251.9879. Selected data of **3ad′**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 4.97 (dd, J = 8.4, 7.2 Hz, 1H), 2.46−2.32 (m, 1H), 2.27−2.14 (m, 1H), 1.62−1.30 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ESI-HRMS calcd for $C_7H_{10}I_2NO$ ($M + H^+$) 377.8846. Found 377.8845.

*4-Iodo-3-phenyl-5-methylisoxazole (**3ae**):*[8a] **3ae** (33.7 mg, 96%) was obtained from **1ae** (40.0 mg, 0.162 mmol). Eluent: hexane/AcOEt = 5/1. Pale yellow crystals; mp 97−99 °C (hexane/AcOEt); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.77 (m, 2H), 7.49−7.47 (m, 3H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 162.8, 130.0, 128.7, 128.5, 128.4, 57.8, 12.9.

4-Bromo-3-phenylisoxazole (4a). To a solution of **2a** (39.0 mg, 0.0958 mmol) in dry CH_2Cl_2 (0.96 mL) was added NBS (25.6 mg, 0.144 mmol) followed by $BF_3 \cdot OEt_2$ (18 μL, 0.144 mmol) at 0 °C and the reaction mixture was stirred for 15 min. The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/AcOEt = 4/1 to give **3a** (1.2 mg, 5%) and **4a** (2.4 mg, 11%). Colorless crystals; mp 53−54 °C (hexane/AcOEt); IR ν_{max}: 3018, 1554 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.88−7.85 (m, 2H), 7.53−7.48 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 158.1, 130.3, 128.7, 128.3, 127.1, 93.3; ESI-HRMS calcd for C_9H_6BrNO ($M+ H^+$) 223.9711. Found 223.9708.

Benzyl 2,5-Dihydro-3-phenyl-4-((trimethylsilyl)ethynyl)-2*H*-isoxazole-2-carboxylate (5). A solution of **2a** (67.0 mg, 0.165 mmol), ethynyltrimethylsilane (26 μL, 0.181 mmol), $PdCl_2(PPh_3)_2$ (1.2 mg, 1.65 μmol), CuI (0.6 mg, 3.29 μmol) in Et_3N (3.0 mL) was stirred for 27 h at rt. After reaction completed, the mixture was diluted with AcOEt, washed with 10% HCl aq., dried over Na_2SO_4, filtered and evaporated in *vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane/AcOEt = 5/1 to give **5** (36.9 mg, 59%) as a yellow oil. IR ν_{max}: 3422, 1754, 1656 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.64 (m, 2H), 7.35−7.33 (m, 3H), 7.25−7.22 (m, 3H), 7.04−7.01 (m, 2H), 5.10 (s, 2H), 4.93 (s, 2H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 144.0, 134.9, 129.5, 129.3, 128.4, 128.23, 128.18, 127.8, 103.9, 103.0, 95.9, 76.0, 68.4, −0.4; ESI-HRMS calcd for $C_{22}H_{24}NO_3Si$ ($M + H^+$) 378.1526. Found 378.1523.

Benzyl 2,5-Dihydro-3-phenyl-4-(2-thienyl)-2*H*-isoxazole-2-carboxylate (6). **2a** (94.1 mg, 0.231 mmol), 2-thiopheneboronic acid (41.4 mg, 0.324 mmol), $Pd(dba)_2$ (6.6 mg, 11.6 μmol), and Ph_3P (12.1 mg, 0.462 mmol) were placed into the Schlenk-flask with reflux condenser and bubble-counter. After THF (1 mL) and 20% Na_2CO_3 aq. (1 mL) were added, the mixture was refluxed for 15 h. It was diluted with AcOEt, and organic layer was separated and evaporated in *vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane/AcOEt = 5/1 to give **6** (53.8 mg, 64%) as a yellow oil. IR ν_{max}: 3021, 1716, 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.36 (m, 5H), 7.26−7.24 (m, 3H), 7.07−7.01 (m, 3H), 6.88 (dd, J = 5.4, 3.6 Hz, 1H), 6.70 (dd, J = 3.6, 1.2 Hz, 1H), 5.35 (s, 2H), 5.06 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 135.0, 132.9, 132.2, 129.7, 129.6, 129.4, 128.6, 128.3, 128.1, 128.0, 126.6, 125.2, 125.0, 112.9, 76.0, 68.0; ESI-HRMS calcd for $C_{21}H_{16}NO_3S$ ($M - H^-$) 362.0851. Found 362.0855.

Benzyl 2,5-Dihydro-4-((*E*)-2-(methoxycarbonyl)ethenyl)-3-phenyl-2*H*-isoxazole-2-carboxylate (7). To a solution of **2a** (56.0 mg, 0.138 mmol), methyl acrylate (45.0 mg, 0.523 mmol), Et_3N (60 μL, 0.414 mmol) in dry CH_3CN (1.5 mL) was added $PdCl_2(PPh_3)_2$ (5.8 mg, 8.30 μmol). The reaction mixture was refluxed for 3 h. After reaction completed, the mixture was quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered and evaporated in *vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane/AcOEt = 2/1 to give **7** (41.8 mg, 83%) as a yellow oil. IR ν_{max}: 3023, 1720, 1619 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.36 (m, 5H), 7.33 (d, J = 15.6 Hz, 1H), 7.27−7.25 (m, 3H), 7.05−7.02 (m, 2H), 5.58 (d, J = 15.6 Hz, 1H), 5.19 (s, 2H), 5.08 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 152.6, 142.2, 134.6, 134.4, 129.9, 129.1, 128.45, 128.39, 128.3, 128.0, 118.6, 115.9, 74.4, 68.5, 51.6; ESI-HRMS calcd for $C_{21}H_{18}NO_5$ ($M - H^-$) 364.1185. Found 364.1189.

Benzyl 2,5-Dihydro-4-((*E*)-2-(methoxycarbonyl)ethenyl)-3-phenyl-5-methyl-2*H*-isoxazole-2-carboxylate (8). According to general procedure for the preparation of 2,5-dihydroisoxazole **2**, **2r** was obtained from **1r** (40.0 mg, 0.135 mmol). Eluent: hexane/Et_2O = 3/1. And then, to a solution of **2r**, methyl acrylate (46 μL, 0.513 mmol), Et_3N (56 μL, 0.405 mmol) in dry CH_3CN (1.5 mL) was added $PdCl_2(PPh_3)_2$ (5.7 mg, 8.10 μmol). The reaction mixture was refluxed for 3 h. After reaction completed, the mixture was quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/AcOEt = 2/1 to give **8** (26.4 mg, 52%) as a yellow oil. IR ν_{max}: 3023, 1720, 1618 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.35 (m, 5H), 7.27 (d, J = 16.0 Hz, 1H), 7.27−7.22 (m, 3H), 7.12 (dd, J = 4.5, 2.0 Hz, 2H), 5.70 (d, J = 16.0 Hz, 1H), 5.43 (q, J = 6.0 Hz, 1H), 5.07 (q, J = 9.5 Hz, 2H), 3.70 (s, 3H), 1.52 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 153.0, 142.3, 134.9, 134.8, 130.0, 129.3, 128.6, 128.5, 128.4, 128.3, 127.9, 120.7, 117.7, 81.9, 68.4, 51.7, 19.8; ESI-HRMS calcd for $C_{22}H_{22}NO_5$ ($M + H^+$) 380.1498. Found 380.1490.

4-(5-Methyl-3-phenyl-isoxazol-4-yl)benzenesulfonamide (Valdecoxib) (9)[18]**.** **3ae** (20.0 mg, 0.0700 mmol), 4-sulphamoylbenzeneboronic acid (19.7 mg, 0.0980 mmol), $Pd(dba)_2$ (2.0 mg, 3.50 μmol), and Ph_3P (3.7 mg, 0.0140 mmol) were placed into the Schlenk-flask with reflux condenser and bubble-counter. After THF (3.7 mL) and 20% Na_2CO_3 aq. (3.7 mL) were added, the mixture was refluxed for 13 h. It was diluted with AcOEt, and organic layer was separated and evaporated in *vacuo*. The residue was purified by flash column chromatography on silica gel eluting with hexane/AcOEt = 5/1 to give **9** (11.8 mg, 54%) as colorless crystals. mp 172−173 °C (hexane/AcOEt); IR ν_{max}: 3379, 3372, 2993, 1359, 1159 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.91 (d, J = 8.7 Hz, 2H), 7.46−7.36 (m, 5H), 7.38 (d, J = 8.7 Hz, 2H), 4.88 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.1, 162.6, 144.5, 135.6, 131.4, 130.9, 130.0, 129.8, 129.6, 127.6, 116.0, 11.5; ESI-HRMS calcd for $C_{16}H_{15}N_2O_3S$ ($M + H^+$) 315.0803. Found 315.0804.

Benzyl 2,5-Dihydro-4-(4-sulfamoylphenyl)-3-phenyl-5-methyl-2*H*-isoxazole-2-carboxylate (*N*-Cbz-2,5-dihydrovaldecoxib) (10). According to general procedure for the preparation of 2,5-dihydroisoxazole **2**, **2r** was obtained from **1r** (25.0 mg, 0.0847 mmol). Eluent: hexane/Et_2O = 3/1. And then, to a solution of **2r**, 4-sulphamoylbenzeneboronic acid (23.8 mg, 0.119 mmol), $Pd(dba)_2$ (2.4 mg, 4.23 μmol), and Ph_3P (4.4 mg, 0.0169 mmol) were placed into the Schlenk-flask with reflux condenser and bubble-counter. After THF (3.6 mL) and 20% Na_2CO_3 aq. (3.6 mL) were added, the mixture was refluxed for 13 h. It was diluted AcOEt, and organic layer was separated and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/AcOEt = 5/1 to give **10** (15.3 mg, 40%) as a colorless oil. IR ν_{max}: 3346, 3276, 3031, 1724, 1597, 1340, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.7 Hz, 2H), 7.36−7.21 (m, 8H), 7.10 (d, J = 8.4 Hz, 2H), 5.80 (q, J = 6.3

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Hz, 1H), 5.09 (s, 2H), 4.89 (s, 2H), 1.47 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 140.2, 137.1, 137.0, 134.9, 129.5, 129.3, 129.1, 128.6, 128.3, 128.2, 127.9, 126.7, 121.6, 84.0, 77.2, 68.2, 19.3; ESI-HRMS calcd for $C_{24}H_{23}N_2O_5S$ ($M + H^+$) 451.1328. Found 451.1325.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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