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One-Pot Synthesis of γ-Azidobutyronitriles and Their Intramolecular Cycloadditions

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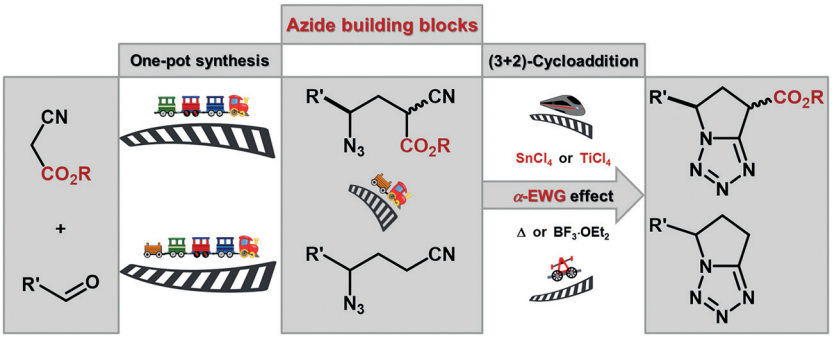

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Abstract Efficient gram-scale, one-pot approaches to azidocyanobutyrates and their amidated or decarboxylated derivatives have been developed, starting from commercially available aldehydes and cyanoacetates. These techniques combine (1) Knoevenagel condensation, (2) Corey–Chaykovsky cyclopropanation and (3) nucleophilic ring opening of donor-acceptor cyclopropanes with the azide ion, as well as (4) Krapcho decarboxylation or (4′) amidation. The synthetic utility of the resulting γ-azidonitriles was demonstrated by their transformation into tetrazoles via intramolecular (3+2)-cycloaddition. A condition-dependent activation effect of the α-substituent was revealed in that case. Thermally activated azide–nitrile interaction did not differentiate the presence of an α-electron-withdrawing substituent in γ-azidonitriles, whereas the Lewis acid mediated ($SnCl_4$ or $TiCl_4$) reaction proceeded much easier for azidocyanobutyrates. This allowed us to develop an efficient procedure for converting azidocyanobutyrates into the corresponding tetrazoles.

Key words azides, nitriles, one-pot synthesis, 1,3-dipolar cycloaddition, tetrazoles, Knoevenagel condensation, Corey–Chaykovsky reaction, nucleophilic ring opening

For rapid access to structurally diverse molecules, versatile building blocks with multiple strategically arranged functional groups are in demand. The synthesis of such functionalized structures starting from commercially available compounds usually includes several steps. Meanwhile, one of the main trends of current organic chemistry is sustainability; i.e., rational step-economic processes that require no isolation of intermediates. Therefore, the development of synthetic strategies based on domino, tandem or one-pot processes that can enhance efficiency and step economy is important and sought-after.[1]

In the last few years, our group has been interested in the nucleophilic ring opening of donor-acceptor cyclopropanes[2] with the azide ion[3] as an efficient approach to highly functionalized azido-substituted building blocks (Scheme 1A).[4] The presence of the azido group in these structures opens numerous ways to their transformations via azide rearrangements, cycloadditions or reduction into a broad variety of N-containing compounds, including *N*-heterocycles. Particularly, azides **3**, simultaneously containing azido, cyano, ester and pronucleophilic CH groups, can be efficiently used for the synthesis of aminopyrrole derivatives and pyrrole-fused polycyclic systems.[4e] A convenient synthetic approach to **3**, starting from commercial aldehydes and cyanoacetates, includes three sequential steps: (*i*) Knoevenagel condensation, (*ii*) Corey–Chaykovsky cyclopropanation and (*iii*) nucleophilic ring opening of a cyclopropane with the azide ion (Scheme 1B). We found that some tuning of the reaction conditions allows for combining these steps into an advanced one-pot process that is viable in terms of time efficiency as well as yields of the target azides **3**.

Moreover, the specific conditions of their subsequent transformations can facilitate further extension of this one-pot process. In this work, Krapcho decarboxylation and amidation were combined with a three-step synthesis of azides **3** within one-pot protocols, affording azidonitriles **4** and amides **5**. The synthetic utility of **3** for the assembly of five-membered *N*-heterocycles is exemplified by intramolecular (3+2)-cycloaddition leading to bicyclic pyrrolotetrazole systems **6** and **7**.

One-Pot Synthesis of γ-Azidobutyronitriles

The feasibility of combining Knoevenagel (*i*), Corey–Chaykovsky (*ii*) and nucleophilic ring opening (*iii*) steps into a one-pot synthesis of azidocyanobutyrates **3** is

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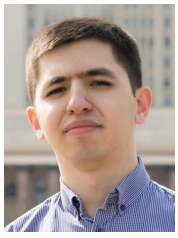
Biographical sketches

Konstantin Ivanov was born in Ulyanovsk, Russia. He graduated from the Department of Chemistry, Lomonosov Moscow State University, in 2012 and received his PhD in organic chemistry in 2016 (PhD thesis 'Nucleophilic Ring Opening of Donor-Acceptor Cyclopropanes with Azide Ion in Synthesis of N-Heterocycles') under the supervision of Dr. Ekaterina Budynina. He is currently a researcher at the Department of Chemistry, Lomonosov Moscow State University. His research is focused on the chemistry of activated cyclopropanes, organic azides, and N-heterocycles, and on DFT calculations.



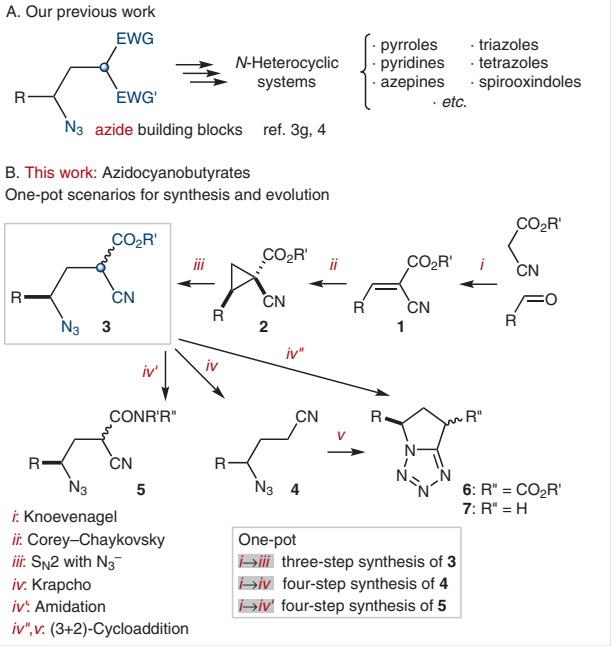
Hamidulla Tukhtaev was born in Tashkent, Uzbekistan. He graduated from the Department of Chemistry of Lomonosov Moscow State University in 2018. Then he worked as a research-intern at the Institute of Bioorganic Chemistry of Academy of Science of Uzbekistan. He joined the research group of Dr. Budynina in 2014. Currently he is a PhD student at Lomonosov Moscow State University. His research is focused on the chemistry of organic azides, aza-Wittig reactions, and the synthesis of N-heterocycles.

Feruza Tukhtaeva was born in Tashkent, Uzbekistan. She received her bachelors degree at the Department of Methods of Teaching Chemistry of Nizami Tashkent State Pedagogical University in 2017 and her Master's degree at the Faculty of Chemistry of Mirzo Ulugbek National University of Uzbekistan in 2019. She worked in the research group of Dr. Budynina in 2019 (on behalf of the Lomonosov Moscow State University student exchange program). She is currently a PhD student at the Laboratory of Heteroatomic Compounds at the Department of Chemistry of Lomonosov Moscow State University. Her research is focused on petrochemistry.

Stanislav Bezzubov is a senior researcher at the Kurnakov Institute of General and Inorganic Chemistry of the Russian Academy of Sciences, Moscow, Russia. After completing his PhD at the Lomonosov Moscow State University he transferred to the Kurnakov Institute in 2015. He worked as a visiting researcher at Durham University (with Prof. Judith Howard) in 2018 and has been in his current position since 2019. His research focuses on cyclometalated Ir(III) and Ru(II) complexes and some aspects of chemical crystallography, including solid-state supramolecular chemistry via crystal engineering.

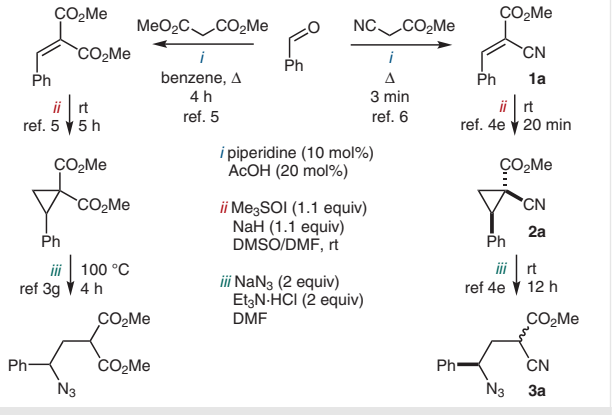
Mikhail Melnikov was born in Moscow, USSR. He graduated from the Department of Chemistry of Lomonosov Moscow State University in 1969. He is a full professor (1991), ScD (1984), and the head of the chair of Chemical Kinetics at Lomonosov Moscow State University. His research is focused on the kinetics and mechanisms of chemical and biological processes, photochemistry, catalysis and nanochemistry.

Ekaterina Budynina was born in Moscow, Russia. She studied chemistry at Lomonosov Moscow State University and received her specialist degree in 2001 and her PhD in 2003. She worked at the University of Nottingham (2004) and Imperial College London (2013) as a visiting researcher. She is currently a leading researcher at the Department of Chemistry, Lomonosov Moscow State University, focusing on the chemistry of activated cyclopropanes.



Scheme 1 Current strategy

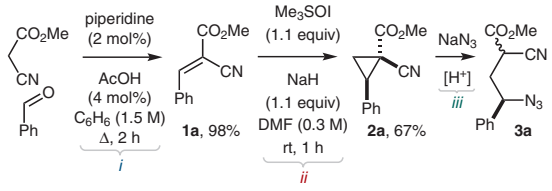
primarily related to mild conditions characteristic of these reactions with cyano-derived precursors (cyanoacetates, cyanoacrylates **1** and cyano-activated cyclopropanes **2**) in contrast to, for example, the malonate derivatives (Scheme 2).[3g,4e,5,6]



Scheme 2 Comparison of the reaction conditions for the synthesis of azidomalonate and azidocyanoester derivatives

The classic Knoevenagel conditions implicate the use of a high percentage of piperidine (up to 10 mol%) and AcOH (up to 20 mol%) as catalytic additives. However, the relative ease of cyanoacrylate **1** formation (for some aldehydes, it even occurs at ambient temperature without azeotrope distillation) allowed us to minimize the amount of the catalyst (Table 1).[6] This, along with rough water removal via azeotrope distillation, provided an opportunity for combining[7] this step with a subsequent Corey–Chaykovsky reaction that requires inert and anhydrous conditions. The cyclopropanation of cyanoacrylate **1a** was completed in 1 h at ambient temperature, leading to cyclopropane **2a** in good yield, predominantly as the more stable *trans*-isomer (dr >95:5).[3a] To optimize the conditions for the third step of our one-pot synthesis of **3a**, a series of experiments was carried out while varying loads of NaN_3 and proton sources, as well as reaction temperature and time (Table 1). According to our previous work, 2 equiv of NaN_3 and 2 equiv of $Et_3N{\cdot}HCl$ as a proton source were used for conversion of **2** into **3**.[4e] In our current work, we initiated optimization while using the same loading of NaN_3 and increasing the loading of $Et_3N{\cdot}HCl$ by 50% to lower the increased basicity after the previous step and shift the equilibrium between **2** and **3**.[3a] This experiment was carried out at room temperature for 12 h and resulted in **3a** in a 59% one-pot yield (entry 1), whereas the three-step yield reported earlier amounted to 52%. The decrease in the loadings of NaN_3 and $Et_3N{\cdot}HCl$ led to an increase in the yield of **3a** (62–67%) (entries 2–4). Similar experiments with NH_4Cl instead of $Et_3N{\cdot}HCl$ led to **3a** with lower yields (55–58%) (entries 5 and 6). A slight increase in temperature (35 °C) also led to a decrease in the yield of **3a** (44–54%) either for $Et_3N{\cdot}HCl$ or NH_4Cl (entries 7 and 8). A further increase in temperature up to 50 °C (entry 9), although allowing for a noticeably reduced reaction time (4 h), afforded **3a** in only a moderate yield (26%). Therefore, the use of 1.3 equiv of NaN_3 and 1.4 equiv of $Et_3N{\cdot}HCl$ at room temperature was found to be optimal for carrying out the third step within this one-pot conversion of cyanoacetate and benzaldehyde into azide **3a** (entry 3).

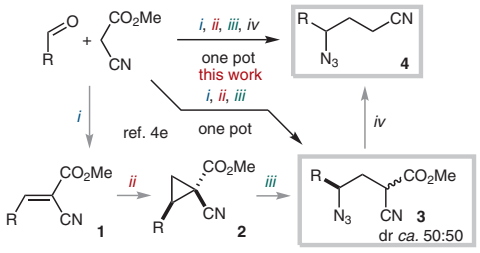
Table 1 Optimization of the Reaction Conditions for the Third Step of the One-Pot Synthesis of Azide **3a**



Entry	NaN_3 (equiv)	$[H^+]$ (equiv)	*T* (°C)	*t* (h)	One-pot yield **3a** (%)
1	2.0	$Et_3N{\cdot}HCl$, 3.0	25	12	59
2	1.7	$Et_3N{\cdot}HCl$, 1.8	25	12	67
3	1.3	$Et_3N{\cdot}HCl$, 1.4	25	12	67
4	1.1	$Et_3N{\cdot}HCl$, 1.2	25	12	62
5	1.7	NH_4Cl, 1.8	25	12	58
6	1.1	NH_4Cl, 1.2	25	12	55
7	1.1	$Et_3N{\cdot}HCl$, 2.2	35	12	54
8	1.1	NH_4Cl, 2.2	35	12	44
9	2.0	$Et_3N{\cdot}HCl$, 2.0	50	4	26

To verify the efficiency of the proposed one-pot procedure, we examined arylcarbaldehydes containing electron-donating and electron-withdrawing groups as well as hetaryl and alkenyl carbaldehydes under the optimized conditions (Table 2). In all cases, the yields of **3** in one-pot syntheses were higher than those achieved in three-distinct-step syntheses. In two cases (**3d** and **3l**), we succeeded in increasing the yields twofold via our one-pot procedure. Moreover, in an appropriate reaction medium, this procedure can be easily combined with Krapcho decarboxylation. In several examples, we demonstrated that a one-pot, four-step procedure involving a Krapcho step led to azidobutyronitriles **4** in 22–44% overall yields. These yields are two to three times higher than those for stepwise procedures.

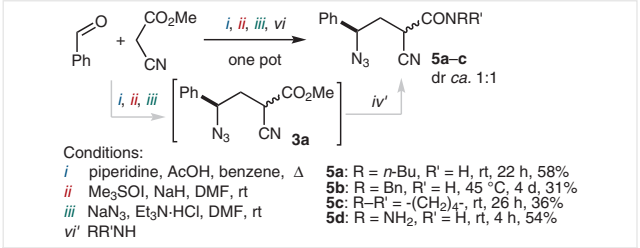
Table 2 One-Pot Synthesis of Azides **3** and **4**[a]



R	3	Yield 3 (%)		4	Yield 4 (%)	
		three-step[b]	one-pot		four-step[b]	one-pot
Ph	**a**	52	67	**a**	21	39
Ph[c]	**b**	36	58			
4-MeC_6H_4	**c**	46	54	**b**	–	44
4-FC_6H_4	**d**	32	64	**c**	–	42
4-ClC_6H_4	**e**	36	41	**d**	–	41
2-ClC_6H_4	**f**	–	53			
4-BrC_6H_4	**g**	45	52	**e**	12	36
4-$MeOC_6H_4$	**h**	34	51	**f**	–	42
3-$MeOC_6H_4$	**i**	–	56			
2,3-$(MeO)_2C_6H_3$	**j**	–	68			
3,4-$(MeO)_2C_6H_3$	**k**	44	51[d]			
3,4,5-$(MeO)_3C_6H_2$	**l**	24	54			
2,4,6-$(MeO)_3C_6H_2$	**m**	–	69[d]			
4-NCC_6H_4	**n**	22	38			
4-$O_2NC_6H_4$	**o**	–	28			
1-Naph	**p**	38	47			
1,4-(C_6H_4)-	**q**	–	50			
(*E*)-styryl	**r**	46	44	**g**	–	22
2-furyl	**s**	26	27			
2-thienyl	**t**	37	50	**h**	–	37
2-(*N*-methyl)indolyl	**u**	–	58			
3-pyridyl				**i**	–	28

[a] Reaction conditions: *i*. Piperidine (2 mol%), AcOH (4 mol%), benzene (1.5 M), reflux, 2.5 h; *ii*. $(CH_3)_3SOI$ (1.1 equiv), NaH (1.1 equiv), DMF (0.3 M), r.t., 1 h; *iii*. NaN_3 (1.3 equiv), $Et_3N{\cdot}HCl$ (1.4 equiv), r.t., 12–16 h; *iv*. LiCl (1.0 equiv), H_2O (4 mL), 125 °C, 3–6 h.
[b] Yields of three- and four-step synthesis are given according to our previous work.[4e]
[c] *t*-Bu ester was used. The yield was estimated for a two-step synthesis of **3b** from styrene and *tert*-butyl cyanoacetate via bromosulfonium bromide.[4e]
[d] Reaction time 24 h.

An additional opportunity to modify azides **3** in a one-pot manner is provided by amidation that can be introduced as the fourth step (Scheme 3). The use of *n*-butylamine, benzylamine and pyrrolidine as aliphatic primary and secondary amines (or, alternatively, hydrazine) led to amide or hydrazide derivatives **5a–d** in 31–58% overall yields. Piperidine unexpectedly gave a quite complex reaction mixture that did not allow for the isolation of the corresponding amide in adequate yield. The use of less nucleophilic aromatic amines, for example, aniline, was found to be inefficient in a one-pot process.



Scheme 3 One-pot synthesis of amides **5** involving the nucleophilic acyl substitution step *iv′*

Intramolecular Cycloadditions

An obvious possibility for the heterocyclization of **3** or **4** using their inherent functionalities is (3+2)-cycloaddition between the azido and cyano groups, affording the assembly of a fused tetrazole core.[8] In contrast to the azide–alkyne click reaction, which allows extremely simple access to triazoles from a broad variety of organic azides and alkynes, tetrazole formation from azides and nitriles proceeds under much harsher conditions and has significant limitations. The tetrazole synthesis via intermolecular (3+2)-cycloadditions can be carried out efficiently only for highly activated nitriles.[9] The intramolecular reactions proceed much more readily for various activated and non-activated azidonitriles containing three-,[10] four-[3g,10a,c,e,i,j,11] and five-atom[12] linkers between the azido and cyano groups. However, even in these cases, high temperature or activation with strong Brønsted or Lewis acids were required. The principal thermally activated reactions were typically carried out under prolonged heating at ≥110 °C in DMSO, DMF, toluene or xylene as solvents. Meanwhile, only a couple of acid-activated reactions were reported with $ClSO_3H$,[10a] H_2SO_4,[10a] TFA,[10l] and $BF_3{\cdot}OEt_2$[10i,j] used as activators at 0–40 °C.

Our attempts to combine the thermal version of (3+2)-cycloaddition with a one-pot synthesis of **3** or **4** led to unsatisfactory yields of the corresponding tetrazoles **6** and **7**

due to significant tarring under these harsh conditions (140–160 °C). Moreover, the conversion of ester derivatives **3** into tetrazoles **6** was complicated by Krapcho decarboxylation.

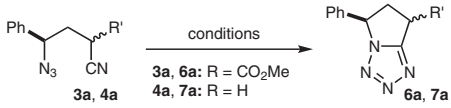
Extremely mild conditions (0 °C to r.t.) for intramolecular tetrazole formation activated by BF_3·OEt_2 were reported by Hanessian and co-workers.[10i,j] We tried to combine our BF_3-mediated (3+2)-cycloaddition with a one-pot synthesis of the initial azides **3** and **4**. However, it was found to be untenable, apparently due to deactivation of a Lewis acid under the studied conditions. Therefore, optimization of the reaction conditions for (3+2)-cycloaddition was carried out for the isolated azides **3a** and **4a**.

Upon heating, (3+2)-cycloaddition for **3a** and **4a** proceeded slowly at ≥130 °C, accompanied by significant tarring (Table 3, entries 1–4, 17, and 18). According to these results, ester **3a** underwent (3+2)-cycloaddition faster than its EWG-free derivative **4a**. Activation with TFA was found to be more efficient, providing slow conversion of **3a** and **4a** into the corresponding tetrazoles **6a** and **7a** in 40 and 48% yields at temperatures as low as 25 °C (entries 5, 6, and 19). A stronger acid, TfOH, caused significant tarring, so that the yield of **3a** did not exceed 25% (entries 7 and 8). Next, we tested BF_3·OEt_2 as an activator while varying reaction temperature and time. We found that the conversion of azides **3a** and **4a** into tetrazoles **6a** and **7a** in the presence of BF_3·OEt_2 (2 equiv) became detectable only at increased temperature (entries 9–11 and 20–23). This is in contrast to the mild conditions reported for intermolecular (3+2)-cycloaddition with participation of less sterically hindered secondary azides.[11h] Interestingly, in DMF, the conversion of **3a** into **6a** was indeed observed but only at increased temperature (140 °C). This implies thermal activation alone without BF_3 participation. The best yields of tetrazoles **6a** (45%) and **7a** (50%) were achieved in 10–11 h when reactions were carried out at 70 °C (entries 10 and 23). An increase in temperature to 90 °C led to a slight decline in the yield of **6a** (entry 11).

To estimate the relative rates of (3+2)-cycloadditions for azides **3** and their ester-free derivatives **4**, we carried out a model experiment using **3a**/**4a** mixture in a 1:1 ratio (Scheme 4A). Quenched in 2 h, the reaction mixture contained azides **3a** and **4a** as well as tetrazoles **6a** and **7a** in a 30:13:30:27 ratio. According to this experiment, the conversion of **3a** was slower than that of **4a**. Therefore, surprisingly, the presence of an ester group that, supposedly, activates the nitrile moiety toward (3+2)-cycloaddition does not accelerate this reaction when BF_3·OEt_2 is used as an activator. Meanwhile, our recent study[4e] related to domino Staudinger/aza-Wittig reaction of azides **3** and **4** revealed that EWG (e.g., an ester group) located at an α-position relative to the CN group plays a crucial activating role (Scheme 4B). Azides **3**, containing an α-CO_2Me group, readily undergo a complete domino Staudinger/aza-Wittig transformation, leading to cyclic iminophosphazenes. However, ester-free azides **4** are only able to undergo the first step of this reaction, yielding acyclic phosphazenes that are not prone to aza-Wittig cyclization.

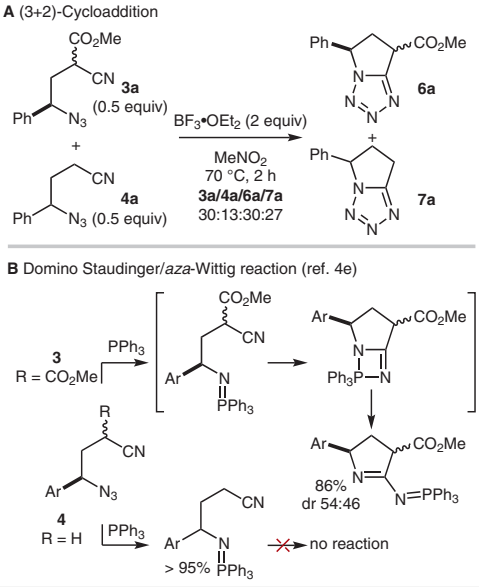
Under activation with BF_3·OEt_2, a short series of azides **3** and **4** containing electron-donating (Me) and electron-withdrawing (F) groups at the aryl substituent was transformed into tetrazoles **6b**,**c** and **7b**,**c** in moderate yields (29–30%) (Table 4). Unfortunately, azide **3h**, containing a *para*-methoxyphenyl (PMP) substituent, underwent signifi-

Table 3 Optimization of Reaction Conditions for (3+2)-Cycloaddition of **3a** and **4a**



Entry	Additive (equiv)	Solvent	*T* (°C)	*t* (h)	Conv. (%)	Yield (%)[d]
R = CO_2Me: **3a** → **6a**						
1	–	DMSO	130[a]	3	12	nd
2	–	DMF	160[a]	6	17	nd
3	–	toluene	150[a]	2.5	20	nd
4	–	toluene	160[a]	2	38	nd
5	–	TFA	r.t.	3	40	nd
6	–	TFA	r.t.	27	>95	40
7	TfOH (1.0)	CH_2Cl_2	r.t.	1	>50	nd[b]
8	TfOH (1.0)	CH_2Cl_2	r.t.	25	>95	25[b]
9	BF_3·OEt_2 (2.0)	DMF	140	4	45	9
10	BF_3·OEt_2 (2.0)	CH_3NO_2	70	11	>95	45
11	BF_3·OEt_2 (2.0)	CH_3NO_2	90	2	>95	40
12	$Zn(OTf)_2$ (0.3)	DCE	80	4	<5	nd
13	$MgBr_2$·OEt_2 (0.2)	CH_3NO_2	101	1	5	nd
14	CuI (0.05)	DMSO	90	5	<5	nd
15	$SnCl_4$ (1.2)	CH_2Cl_2	r.t.	12	>95	88
16	$TiCl_4$ (1.2)	CH_2Cl_2	r.t.	12	>95	86
R = H: **4a** → **7a**						
17	–	DMSO	160[a]	43	20	17[b]
18	–	toluene	150[a]	2.5	8	nd
19	–	TFA	r.t.	36	>95	48
20	BF_3·OEt_2 (2.0)	$MeNO_2$	50	4	38	nd
21	BF_3·OEt_2 (2.0)	$MeNO_2$	60[a]	16	90	nd
22	BF_3·OEt_2 (2.0)	$MeNO_2$	60	33	>95	53
23	BF_3·OEt_2 (2.0)	$MeNO_2$	70	10	>95	50
24	$SnCl_4$ (1.2)	CH_2Cl_2	r.t.	120	95	39[c]

[a] Microwave heating.
[b] Significant tarring was observed.
[c] **4b** → **7b** transformation was studied.
[d] nd – not determined.



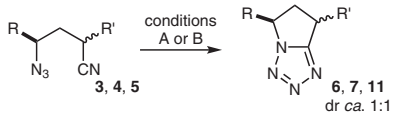
Scheme 4 Relative reactivities of **3a** and **4a** in (3+2)-cycloaddition (**A**); comparison with reactivities in domino Staudinger/aza-Wittig reaction (**B**)

cant tarring under the studied conditions (see comment to Scheme 5) and, thus, only gave tetrazole **6g** in 14% yield. For compounds **7a–c**, which were found to be easily crystallizable, single-crystal X-ray analysis was carried out.

Under identical conditions, azide **4f**, with a PMP substituent, gave pyrrolotetrazole **7d** as a minor product, while the alkylated derivative **8** was found to be the major product (Scheme 5A). The formation of **8** can be associated with intermediate formation of the PMP-stabilized benzylic cation (supposedly, as a tight ion pair with N_3^-) with the corresponding styrene undergoing further dimerization afterwards (Scheme 5B). The proposed mechanism is in accordance with the precedent of *para*-methoxybenzylic cation formation from *para*-methoxybenzylazide.[13] Moreover, the moderate yields of other tetrazoles **6** and **7** (particularly, those containing electron-donating stabilizing groups) can also be explained by the formation of the proposed intermediates and their further oligomerization.

In the case of 2 mmol-scale synthesis of tetrazole **7a**, isomeric tetrazole **7′a** could be isolated in 2% yield along with the main product (Scheme 6A). The presence of trace amounts of tetrazoles **7′** was detected in all reaction mixtures after (3+2)-cycloaddition of azides **4**. Tetrazoles **7′** were probably formed from isomeric azides **4′** that were present in trace amounts in the reaction mixtures upon Krapcho decarboxylation of azidoesters **3**. Apparently, under Krapcho conditions, there is an equilibrium between azides **3** (attack on C2) and **3′** (attack on C3), the precursors of **4** and **4′**, respectively, via cyclopropanes **2**. For the

Table 4 Scope of Lewis Acid Activated (3+2)-Cycloaddition[a]



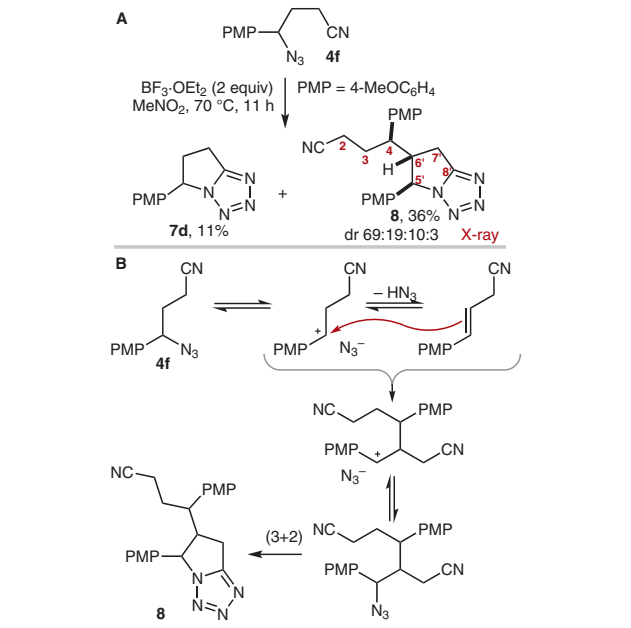
Product	R	R′	Yield (conditions A; %)	Yield (conditions B; %)
6a	Ph	CO_2Me	45	88
6b	4-MeC_6H_4	CO_2Me	47	84
6c	4-FC_6H_4	CO_2Me	52	92
6d	4-ClC_6H_4	CO_2Me	–[b]	90
6e	2-ClC_6H_4	CO_2Me	–[b]	92
6f	4-BrC_6H_4	CO_2Me	–[b]	94
6g	4-$MeOC_6H_4$	CO_2Me	14	36
6h	3-$MeOC_6H_4$	CO_2Me	–[b]	90
6i	4-NCC_6H_4	CO_2Me	–[b]	86[c]
6j	4-$O_2NC_6H_4$	CO_2Me	–[b]	85[c]
6k	1-naphthyl	CO_2Me	–[b]	89
6l	2-thienyl	CO_2Me	–[b]	18
6m	Ph	CONHBu	–[b]	90
7a[d]	Ph	H	50	–[b]
7b[d]	4-MeC_6H_4	H	29	39[e]
7c[d]	4-FC_6H_4	H	30	–[b]

[a] Reaction conditions A: BF_3·OEt_2 (2 equiv), $MeNO_2$, 70 °C, 11 h. Reaction conditions B: $SnCl_4$ (1.2 equiv), DCM, 25 °C, 6–12 h.
[b] Reaction was not carried out under these conditions
[c] Reaction time: 24 h.
[d] Single-crystal X-ray analysis was carried out
[e] Reaction time: 120 h.

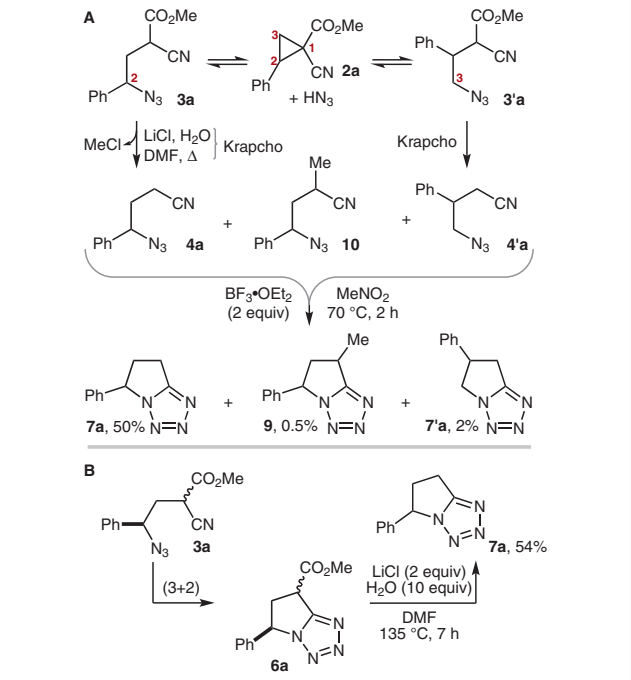
malonate analogue of **2a**, dimethyl 2-phenylcyclopropane-1,1-dicarboxylate, the S_N2-like attack on C2 is favored over that on C3 ($\Delta G^{\neq}$ = 6.6 kcal/mol).[3g] However, the thermodynamic stabilities of the resulting azides are comparable. Additionally, the signals of methylated derivative **9** were detected in ^1H NMR and HRMS spectra. The resulting product **9** is apparently formed by (3+2)-cycloaddition within azide **10**, formed upon the alkylation of the initial azide **3a** with MeCl (or its analogue), produced by the elimination of MeCl from **3a** under the Krapcho conditions.

Switching the order of the steps (the azide **3a** undergoing (3+2)-cycloaddition followed by Krapcho decarboxylation of tetrazole **6a**) allowed us to avoid the formation of isomer **7′a** (Scheme 6B).

The examination of other potential activators of (3+2)-cycloaddition revealed that weak Lewis acids (e.g., $Zn(OTf)_2$ or BF_3·OEt_2) did not induce noticeable **3a**→**6a** conversion, even at increased temperature (Table 3, entries 12 and 13). The commonly used CuI also did not catalyze this reaction (entry 14). However, strong Lewis acids ($SnCl_4$ and $TiCl_4$)



Scheme 5 Formation of side product **8** in (3+2)-cycloaddition of azide **4f** containing an electron-donating aryl substituent PMP

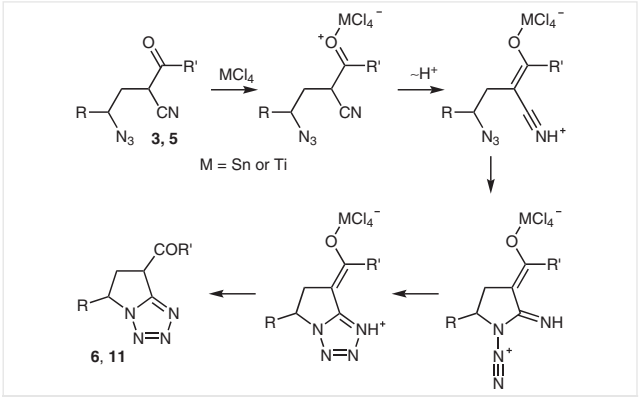


Scheme 6 Formation of side products **7′a** and **9** in the synthesis of **7a** (A); alternative approach to **7a** (B)

that are conventionally used to trigger Schmidt rearrangement,[14] but not (3+2)-cycloaddition, were found to activate **3a** toward the assembly of tetrazole **6a** in yields that were twice as high as those in the case of activation with BF_3·OEt_2 (entries 15 and 16). Encouraged by these results, we carried out $SnCl_4$-activated (3+2)-cycloaddition for a representative series of azides **3** with various (het)aryl substituents R (Table 4). Overall, tetrazoles **6** were obtained in high yields (84–94%). For example, 4-chlorophenyl-substituted azide **3e** and its isomer **3f**, with a sterically hindered 2-chlorophenyl substituent, gave the corresponding tetrazoles **6d** and **6e** with the same efficiency. However, similar to the BF_3-activated tetrazole synthesis, the transformation of PMP-substituted azide **3h** provided one of the exceptions, affording tetrazole **6g** in a low yield (36%). The decay of chemoselectivity in this case could also be associated with the possibility for easier generation of benzylic cations (potentially stabilized by an electron-donating PMP group,[13] see the discussion of Scheme 6). At the same time, the isomeric azide **3i**, with a 3-methoxyphenyl substituent that lacks the ability to stabilize cationic species efficiently, was converted into tetrazole **6h** in a 90% yield. Azide **3t**, with an electron-donating 2-thienyl group, also gave tetrazole **6l** in low yield (18%). The slowest **3**→**6** conversion (24 h) was observed for azides **3n** and **3o** containing the CN and NO_2 groups in their aryl fragments. This deceleration could be related to partial coordination of $SnCl_4$ with these groups.

Similarly, amide **5a** was easily transformed into tetrazole **6m** in 90% yield under activation with $SnCl_4$ (Table 4). Meanwhile, under identical conditions, the ester-free analogues **4** undergo (3+2)-cycloaddition much less efficiently. Thus, the model azide **4b** was converted into tetrazole **7b** in five days with only 39% yield (Table 3, entry 24; Table 4).

It is accepted that, when performed at elevated temperature, the reaction between azides and nitriles proceeds via a concerted mechanism, whereas acidic activation allows for switching to the stepwise pathway.[9b] Efficient $SnCl_4$- or $TiCl_4$-activation of ester- or amide-substituted azides **3** and **5** in comparison with carbonyl-free analogues **4** could be associated with intermediate formation of reactive tin or titanium enolate that undergoes stepwise (3+2)-cycloaddition via an initial attack of an azido group on the activated cyano group, followed by 1,5-cyclization (Scheme 7).



Scheme 7 Proposed mechanism for MCl_4-activated (M = Sn or Ti) (3+2)-cycloaddition of carbonyl-containing azides **3** and **5**

In this work, we developed an efficient one-pot approach to γ-azidocyanobutyrates and their decarboxylated or amidated derivatives starting from commercially available aldehydes and cyanoacetates. Our basic technique, combining the widely used Knoevenagel and Corey–Chaykovsky reactions as well as nucleophilic ring opening of the forming donor-acceptor cyclopropanes with the azide ion, results in γ-azidocyanobutyrates and can be followed by Krapcho decarboxylation or amidation. The synthetic utility of the resulting compounds for the assembly of five-membered aza-heterocycles is exemplified by intramolecular (3+2)-cycloaddition, affording pyrrolotetrazole derivatives. Thermal activation at this step was shown to be inefficient for both γ-azidocyanobutyrates and their decarboxylated derivatives. Meanwhile, Lewis acid triggered reactions led to the target tetrazoles in moderate to high yields. Among the studied Lewis acids, $SnCl_4$ and $TiCl_4$ were found to be the most powerful, inducing specific acceleration of (3+2)-cycloadition for ester-substituted γ-azidonitriles. This allowed us to develop highly efficient synthesis of pyrrolotetrazoles.

Reagents were purchased from commercial sources and used without further purification. NMR spectra were acquired with Bruker Avance 600 MHz spectrometers at r.t.; the chemical shifts (δ) were measured in ppm with respect to solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm; ^{13}C: $CDCl_3$, δ = 77.0 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet; dd, double doublet. Coupling constants (*J*) are given in hertz (Hz). The structures of compounds were elucidated with the aid of 1D NMR (^{1}H, ^{13}C) and 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HSQC and HMBC) spectroscopy. High-resolution and accurate mass measurements were carried out with a BrukermicroTOF-QTM ESI-TOF (Electro Spray Ionization / Time of Flight) and Thermo ScientificTM LTQ Orbitrap mass spectrometers. Melting points (mp) were determined with an Electrothermal IA 9100 capillary melting point apparatus. Microwave reactions were performed with a Monowave 300-Anton Paar microwave reactor in sealed reaction vessels. Analytical thin-layer chromatography (TLC) was carried out with silica gel plates (silica gel 60, F254, supported on aluminium) visualized with UV lamp (254 nm). Column chromatography was performed on silica gel 60 (230–400 mesh). PE = petroleum ether.

One-Pot Synthesis of 4-Azido-2-cyanobutyrates 3

A mixture of the corresponding aldehyde (30 mmol), methyl cyanoacetate (2.97 g, 30 mmol), piperidine (60 μL, 0.60 mmol) and acetic acid (70 μL 1.2 mmol) in benzene (40 mL) was heated to reflux with a 20-mL Dean–Stark trap for 2.5 h. The reaction mixture was cooled to ambient temperature and then to 0 °C in an ice-water bath. The suspension of dimethylsulfoxonium methylide in anhydrous DMF (100 mL), generated from NaH (1.32 g, 33 mmol, 60% suspension in mineral oil), and Me_3SOI (7.26 g, 33 mmol) was added dropwise during 10 minutes under vigorous stirring. The reaction mixture was then allowed to warm to r.t. and stirred for 1 hour. To the resulting mixture, NaN_3 (2.54 g, 39 mmol) and Et_3N·HCl (5.78 g, 42 mmol) were sequentially added. The resulting suspension was stirred at ambient temperature for 12–16 h (**mixture A**), diluted with brine (200 mL) and extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with water (3 × 100 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE–EtOAc). Spectral data for azides **3a–e**, **3g**, **3h**, **3k**, **3l**, **3n**, **3p**, and **3r–t** are consistent with those reported previously.[4e]

Methyl 4-Azido-2-cyano-4-phenylbutyrate (3a)[4e]

Obtained from benzaldehyde (3.18 g).

Yield: 4.89 g (67%); dr **A**/**B** 56:44; yellow oil; R_f = 0.47 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.20 (ddd, ^2J = 14.1, ^3J = 10.3, ^3J = 4.3 Hz, 1 H, CH_2, **A**), 2.36 (ddd, ^2J = 14.0, ^3J = 6.9, ^3J = 6.8 Hz, 1 H, CH_2, **B**), 2.40 (ddd, ^2J = 14.0, ^3J = 8.5, ^3J = 7.0 Hz, 1 H, CH_2, **B**), 2.41 (ddd, ^2J = 14.1, ^3J = 10.8, ^3J = 5.0 Hz, 1 H, CH_2, **A**), 3.52 (dd, ^3J = 7.0, ^3J = 6.9, Hz, 1 H, C^{2}H, **B**), 3.81 (s, 3 H, CH_3O, **A**), 3.83 (s, 3 H, CH_3O, **B**), 3.86 (dd, ^3J = 10.3, ^3J = 5.0, Hz, 1 H, C^{2}H, **A**), 4.74 (dd, ^3J = 8.5, ^3J = 6.8 Hz, 1 H, C^{4}H, **B**), 4.76 (dd, ^3J = 10.8, ^3J = 4.3 Hz, 1 H, C^{4}H, **A**), 7.35–7.37 (m, 2 + 2 H, Ph, **A**, **B**), 7.39–7.41 (m, 1 + 1 H, Ph, **A**, **B**), 7.43–7.46 (m, 2 + 2 H, Ph, **A**, **B**).

tert-Butyl 4-Azido-2-cyano-4-phenylbutyrate (3b)[4e]

Obtained from benzaldehyde (5.73 g, 54.0 mmol) and *tert*-butyl cyanoacetate (6.16 g, 54.0 mmol).

Yield: 8.97 g (58%); dr **A**/**B** 56:44; yellow oil; R_f = 0.62 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.50 (s, 9 H, CH_3, **A**), 1.53 (s, 9 H, CH_3, **B**), 2.14 (ddd, ^2J = 14.1, ^3J = 10.4, ^3J = 4.0 Hz, 1 H, CH_2, **A**), 2.30 (ddd, ^2J = 14.0, ^3J = 7.0, ^3J = 6.7 Hz, 1 H, CH_2, **B**), 2.34 (ddd, ^2J = 14.1, ^3J = 11.0, ^3J = 5.1 Hz, 1 H, CH_2, **A**), 2.37 (ddd, ^2J = 14.0, ^3J = 8.6, ^3J = 7.0 Hz, 1 H, CH_2, **B**), 3.40 (dd, ^3J = 7.0, ^3J = 7.0 Hz, 1 H, C^{2}H, **B**), 3.72 (dd, ^3J = 10.4, ^3J = 5.1 Hz, 1 H, C^{2}H, **A**), 4.72 (dd, ^3J = 8.6, ^3J = 6.7 Hz, 1 H, C^{4}H, **B**), 4.75 (dd, ^3J = 11.0, ^3J = 4.0 Hz, 1 H, C^{4}H, **A**), 7.35–7.37 (m, 2 + 2 H, Ph, **A**, **B**), 7.39–7.41 (m, 1 + 1 H, Ph, **A**, **B**), 7.43–7.46 (m, 2 + 2 H, Ph, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(*p*-tolyl)butyrate (3c)[4e]

Obtained from *p*-tolualdehyde (3.60 g).

Yield: 4.22 g (54%); dr **A**/**B** 54:46; yellow oil; R_f = 0.56 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.18 (ddd, ^2J = 14.1, ^3J = 10.2, ^3J = 4.3 Hz, 1 H, CH_2, **A**), 2.33 (ddd, ^2J = 14.0, ^3J = 7.0, ^3J = 6.9 Hz, 1 H, CH_2, **B**), 2.38 (s, 3 + 3 H, CH_3, **A**, **B**), 2.38–2.43 (m, 1 + 1 H, CH_2, **A**, **B**), 3.51 (dd, ^3J = 7.0, ^3J = 6.9 Hz, 1 H, C^{2}H, **B**), 3.80 (s, 3 H, CH_3O, **A**), 3.82 (dd, ^3J = 10.2, ^3J = 5.1 Hz, 1 H, C^{2}H, **A**), 3.84 (s, 3 H, CH_3O, **B**), 4.70 (dd, ^3J = 8.5, ^3J = 6.9 Hz, 1 H, C^{4}H, **B**), 4.73 (dd, ^3J = 10.8, ^3J = 4.3 Hz, 1 H, C^{4}H, **A**), 7.22–7.26 (m, 4 + 4 H, Ar, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(4-fluorophenyl)butyrate (3d)[4e]

Obtained from 4-fluorobenzaldehyde (3.72 g).

Yield: 5.04 g (64%); dr **A**/**B** 55:45; yellow oil; R_f = 0.66 (PE–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.17 (ddd, ^2J = 14.1, ^3J = 10.4, ^3J = 4.1 Hz, 1 H, CH_2, **A**), 2.32 (ddd, ^2J = 14.1, ^3J = 7.2, ^3J = 6.4 Hz, 1 H, CH_2, **B**), 2.35–2.41 (m, 1 + 1 H, CH_2, **A**, **B**), 3.52–3.55 (m, 1 H, C^{2}H, **B**), 3.82 (s, 3 H, OCH_3, **A**), 3.84 (dd, ^3J = 10.4, ^3J = 4.9 Hz, 1 H, C^{2}H, **A**), 3.87 (s, 3 H, OCH_3, **B**), 4.74 (dd, ^3J = 8.8, ^3J = 6.4 Hz, 1 H, C^{4}H, **B**), 4.76 (dd, ^3J = 11.0, ^3J = 4.1 Hz, 1 H, C^{4}H, **A**), 7.12–7.15 (m, 2 + 2 H, Ar, **A**, **B**), 7.34–7.37 (m, 2 + 2 H, Ar, **A**, **B**).

Methyl 4-Azido-4-(4-chlorophenyl)-2-cyanobutyrate (3e)[4e]

Obtained from 4-chlorobenzaldehyde (4.21 g).

Yield: 3.43 g (41%); dr **A**/**B** 48:52; yellow oil; R_f = 0.45 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.16 (ddd, ^2J = 14.1, ^3J = 10.3, ^3J = 4.1 Hz, 1 H, CH_2, **A**), 2.30 (ddd, ^2J = 14.1, ^3J = 7.1, ^3J = 6.3 Hz, 1 H, CH_2, **B**), 2.35 (ddd, ^2J = 14.1, ^3J = 10.9, ^3J = 5.0 Hz, 1 H, CH_2, **A**), 2.36 (ddd, ^2J = 14.1,

^3J = 8.9, ^3J = 6.6 Hz, 1 H, CH_2, **B**), 3.54 (dd, ^3J = 7.1, ^3J = 6.6 Hz, 1 H, C^2H, **B**), 3.79 (s, 3 H, OCH_3, **A**), 3.82 (dd, ^3J = 10.3, ^3J = 5.0 Hz, 1 H, C^2H, **A**), 3.84 (s, 3 H, OCH_3, **B**), 4.73 (dd, ^3J = 8.9, ^3J = 6.3 Hz, 1 H, C^4H, **B**), 4.74 (dd, ^3J = 10.9, ^3J = 4.1 Hz, 1 H, C^4H, **A**), 7.29–7.32 (m, 2 + 2 H, Ar, **A**, **B**), 7.39–7.42 (m, 2 + 2 H, Ar, **A**, **B**).

Methyl 4-Azido-4-(2-chlorophenyl)-2-cyanobutyrate (3f)

Obtained from 2-chlorobenzaldehyde (4.21 g).

Yield: 4.44 g (53%); dr **A**/**B** 50:50; yellow oil; R_f = 0.68 (PE–EtOAc, 2:1).

^1H NMR ($CDCl_3$, 600 MHz): δ = 2.25–2.28 (m, 2 H, CH_2, **A**), 2.28 (ddd, ^2J = 14.3, ^3J = 9.7, ^3J = 5.4 Hz, 1 H, CH_2, **B**), 2.44 (ddd, ^2J = 14.3, ^3J = 7.8, ^3J = 4.6 Hz, 1 H, CH_2, **B**), 3.72 (dd, ^3J = 7.8, ^3J = 5.4 Hz, 1 H, C^2H, **B**), 3.82 (s, 3 H, OCH_3, **A**), 3.84–3.86 (m, 1 H, C^2H, **A**), 3.88 (s, 3 H, OCH_3, **B**), 5.31 (dd, ^3J = 9.7, ^3J = 4.6 Hz, 1 H, C^4H, **B**), 5.32 (dd, ^3J = 7.8, ^3J = 6.2 Hz, 1 H, C^4H, **A**), 7.31–7.34 (m, 1 + 1 H, Ar, **A**, **B**), 7.36–7.39 (m, 1 + 1 H, Ar, **A**, **B**), 7.43–7.45 (m, 1 + 1 H, Ar, **A**, **B**), 7.48–7.51 (m, 1 + 1 H, Ar, **A**, **B**).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.1 (C^2H), 34.7 (C^2H), 35.0 (CH_2), 35.1 (CH_2), 53.66 (OCH_3), 53.7 (OCH_3), 59.50 (C^4H), 59.52 (C^4H), 115.4 (CN), 115.6 (CN), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 129.96 (CH), 130.01 (CH), 130.1 (2 × CH), 132.78 (C), 132.83 (C), 135.4 (C), 135.5 (C), 165.7 (CO_2Me), 165.8 (CO_2Me).

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{12}H_{10}ClN_4O_2^-$: 277.0498; found: 277.0496.

Methyl 4-Azido-4-(4-bromophenyl)-2-cyanobutyrate (3g)[4e]

Obtained from 4-bromobenzaldehyde (5.55 g).

Yield: 5.07 g (52%); dr **A**/**B** 57:43; yellow oil; R_f = 0.41 (PE–EtOAc, 4:1).

^1H NMR ($CDCl_3$, 600 MHz): δ = 2.16 (ddd, ^2J = 14.1, ^3J = 10.4, ^3J = 4.1 Hz, 1 H, CH_2, **A**), 2.33 (ddd, ^2J = 14.1, ^3J = 7.1, ^3J = 6.4 Hz, 1 H, CH_2, **B**), 2.36 (ddd, ^2J = 14.1, ^3J = 11.0, ^3J = 4.9 Hz, 1 H, CH_2, **A**), 2.37 (ddd, ^2J = 14.1, ^3J = 8.8, ^3J = 6.7 Hz, 1 H, CH_2, **B**), 3.53 (dd, ^3J = 7.1, ^3J = 6.7 Hz, 1 H, C^2H, **B**), 3.82 (s, 3 H, OCH_3, **A**), 3.84 (dd, ^3J = 10.4, ^3J = 4.9 Hz, 1 H, C^2H, **A**), 3.87 (s, 3 H, OCH_3, **B**), 4.72 (dd, ^3J = 8.8, ^3J = 6.4 Hz, 1 H, C^4H, **B**), 4.74 (dd, ^3J = 11.0, ^3J = 4.1 Hz, 1 H, C^4H, **A**), 7.24–7.26 (m, 2 + 2 H, Ar, **A**, **B**), 7.56–7.59 (m, 2 + 2 H, Ar, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(4-methoxyphenyl)butyrate (3h)[4e]

Obtained from *p*-anisaldehyde (4.08 g).

Yield: 4.21 g (51%); dr **A**/**B** 56:44; yellow oil; R_f = 0.30 (PE–EtOAc, 4:1).

^1H NMR ($CDCl_3$, 600 MHz): δ = 2.17 (ddd, ^2J = 14.1, ^3J = 10.2, ^3J = 4.3 Hz, 1 H, CH_2, **A**), 2.33 (m, 1 H, CH_2, **B**), 2.39 (ddd, ^2J = 14.0, ^3J = 8.4, ^3J = 7.3 Hz, 1 H, CH_2, **B**), 2.43 (ddd, ^2J = 14.1, ^3J = 10.8, ^3J = 5.1 Hz, 1 H, CH_2, **A**), 3.49 (dd, ^3J = 7.3, ^3J = 6.9 Hz, 1 H, C^2H, **B**), 3.81 (s, 3 H, OCH_3, **A**), 3.82 (dd, ^3J = 10.2, ^3J = 5.1 Hz, 1 H, C^2H, **A**), 3.84 (s, 3 + 3 H, OCH_3, **A**, **B**), 3.85 (s, 3 H, OCH_3, **B**), 4.69 (dd ^3J = 8.4, ^3J = 7.2 Hz, 1 H, C^4H, **B**), 4.72 (dd, ^3J = 10.8, ^3J = 4.3 Hz, 1 H, C^4H, **A**), 6.94–6.96 (m, 2 + 2 H, Ar, **A**, **B**), 7.27–7.30 (m, 2 + 2 H, Ar, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(3-methoxyphenyl)butyrate (3i)

Obtained from *m*-anisaldehyde (4.08 g).

Yield: 4.61 g (56%); dr **A**/**B** 56:44; yellow oil; R_f = 0.73 (PE–EtOAc, 2:1).

^1H NMR ($CDCl_3$, 600 MHz): δ = 2.17 (ddd, ^2J = 14.1, ^3J = 10.2, ^3J = 4.3, Hz, 1 H, CH_2, **A**), 2.32 (m, 1 H, CH_2, **B**), 2.38 (ddd, ^2J = 14.0, ^3J = 8.5, ^3J = 7.3 Hz, 1 H, CH_2, **B**), 2.39 (ddd, ^2J = 14.1, ^3J = 10.8, ^3J = 5.0 Hz, 1 H, CH_2, **A**), 3.52 (m, 1 H, C^2H, **B**), 3.78 (s, 3 H, OCH_3, **A**), 3.78–3.80 (m, 1 H, C^2H, **A**), 3.81 (s, 3 + 3 H, OCH_3, **A**, **B**), 3.82 (s, 3 H, OCH_3, **A**), 4.70 (dd, ^3J = 8.5, ^3J = 6.8 Hz, 1 H, C^4H, **B**), 4.72 (dd, ^3J = 10.8, ^3J = 4.3 Hz, 1 H, C^4H, **A**), 6.85–6.96 (m, 3 + 3 H, Ar, **A**, **B**), 7.30–7.35 (m, 1 + 1 H, Ar, **A**, **B**).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.1 (C^2H), 34.6 (C^2H), 35.5 (CH_2), 35.9 (CH_2), 53.48 (OCH_3), 53.53 (OCH_3), 55.1 (2 × OCH_3), 62.8 (C^4H), 62.9 (C^4H), 112.4 (2 × CH), 114.3 (CH), 114.4 (CH), 115.6 (2 × CN), 118.9 (2 × CH), 130.1 (CH), 130.2 (CH), 138.5 (C), 138.8 (C), 160.0 (C), 160.1 (C), 165.67 (CO_2Me), 165.70 (CO_2Me).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{15}N_4O_3^+$: 275.1139; found: 275.1135.

Methyl 4-Azido-2-cyano-4-(2,3-dimethoxyphenyl)butyrate (3j)

Obtained from 2,3-dimethoxybenzaldehyde (4.98 g).

Yield: 6.25 g (68%); dr **A**/**B** 55:45; yellow oil; R_f = 0.57 (PE–EtOAc, 1:2).

^1H NMR ($CDCl_3$, 600 MHz): δ = 2.16 (ddd, ^2J = 14.0, ^3J = 10.2, ^3J = 4.1 Hz, 1 H, CH_2, **A**), 2.34–2.38 (m, 2 H, CH_2, **B**), 2.39 (ddd, ^2J = 14.0, ^3J = 10.6, ^3J = 5.1 Hz, 1 H, CH_2, **A**), 3.59–3.61 (m, 1 H, C^2H, **B**), 3.77 (s, 3 H, OCH_3, **A**), 3.79 (dd, ^3J = 10.2, ^3J = 5.1 Hz, 1 H, C^2H, **A**), 3.81 (s, 3 H, OCH_3, **B**), 3.86 (s, 6 H, 2 × OCH_3, **B**), 3.88 (s, 3 H, OCH_3, **A**), 3.89 (s, 3 H, OCH_3, **A**), 5.12–5.14 (m, 1 H, C^4H, **B**), 5.15 (dd, ^3J = 10.6, ^3J = 4.1 Hz, 1 H, C^4H, **A**), 6.90–6.95 (m, 2 + 2 H, Ar, **A**, **B**), 7.08–7.11 (m, 1 + 1 H, Ar, **A**, **B**).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 34.3 (C^2H), 34.6 (C^2H), 34.9 (CH_2), 35.0 (CH_2), 53.4 (2 × OCH_3), 55.6 (2 × OCH_3), 57.09 (OCH_3), 57.15 (OCH_3), 60.9 (2 × C^4H), 112.7 (2 × CH), 115.6 (CN), 115.7 (CN), 118.3 (CH), 118.4 (CH), 124.4 (CH), 124.5 (CH), 130.5 (C), 130.8 (C), 146.4 (C), 146.6 (C), 152.56 (C), 152.59 (C), 165.75 (CO_2Me), 165.76 (CO_2Me).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{17}N_4O_4^+$: 305.1244; found: 305.1240.

Methyl 4-Azido-2-cyano-4-(3,4-dimethoxyphenyl)butyrate (3k)[4e]

Obtained from 3,4-dimethoxybenzaldehyde (4.98 g).

Yield: 4.69 g (51%); dr **A**/**B** 52:48; yellow oil; R_f = 0.44 (PE–EtOAc, 2:1).

^1H NMR ($CDCl_3$, 600 MHz): δ = 2.18 (ddd, ^2J = 14.1, ^3J = 10.2, ^3J = 4.3 Hz, 1 H, CH_2, **A**), 2.32 (m, 1 H, CH_2, **B**), 2.38 (ddd, ^2J = 14.0, ^3J = 8.2, ^3J = 7.3 Hz, 1 H, CH_2, **B**), 2.39 (ddd, ^2J = 14.1, ^3J = 10.8, ^3J = 5.1 Hz, 1 H, CH_2, **A**), 3.48 (dd, ^3J = 7.3, ^3J = 7.2 Hz, 1 H, C^2H, **B**), 3.80 (s, 3 H, OCH_3, **A**), 3.81 (dd, ^3J = 10.2, ^3J = 5.1 Hz, 1 H, C^2H, **A**), 3.84 (s, 3 H, OCH_3, **B**), 3.90 (s, 6 H, 2 × OCH_3, **A**), 3.91 (s, 6 H, 2 × OCH_3, **B**), 4.67 (dd, ^3J = 8.2, ^3J = 7.2 Hz, 1 H, C^4H, **B**), 4.69 (dd, ^3J = 10.8, ^3J = 4.3 Hz, 1 H, C^4H, **A**), 6.83–6.85 (m, 1 + 1 H, Ar, **A**, **B**), 6.88–6.92 (m, 2 + 2 H, Ar, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(3,4,5-trimethoxyphenyl)butyrate (3l)[4e]

Obtained from 3,4,5-trimethoxybenzaldehyde (5.89 g).

Yield: 5.40 g (54%); dr **A**/**B** 59:41; yellow oil; R_f = 0.42 (PE–EtOAc, 2:1).

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.18 (ddd, ^2J = 14.1, ^3J = 10.3, ^3J = 4.2 Hz, 1 H, CH_2, **A**), 2.28–2.33 (m, 1 H, CH_2, **B**), 2.35 (ddd, ^2J = 14.1, ^3J = 10.9, ^3J = 4.9 Hz, 1 H, CH_2, **A**), 2.37 (ddd, ^2J = 14.0, ^3J = 8.4, ^3J = 7.2 Hz, 1 H, CH_2, **B**), 3.51 (dd, ^3J = 7.2, ^3J = 7.0 Hz, 1 H, C^2H, **B**), 3.82 (s, 3 H, OCH_3, **A**), 3.83 (dd, ^3J = 10.3, ^3J = 4.9 Hz, 1 H, C^2H, **A**), 3.86 (s, 9 H, 3 × OCH_3), 3.89 (s, 12 H, 4 × OCH_3), 4.67 (dd, ^3J = 8.4, ^3J = 7.0 Hz, 1 H, C^4H, **B**), 4.69 (dd, ^3J = 10.9, ^3J = 4.2 Hz, 1 H, C^4H, **A**), 6.54–6.56 (m, 2 + 2 H, Ar, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(2,4,6-trimethoxyphenyl)butyrate (3m)

Obtained from 2,4,6-trimethoxybenzaldehyde (5.89 g).

Yield: 6.94 g (69%); dr **A**/**B** 54:46; yellow oil; R_f = 0.52 (PE–EtOAc, 2:1).

^1H NMR ($CDCl_3$, 600 MHz): δ = 2.29 (ddd, ^2J = 13.9, ^3J = 9.3, ^3J = 5.8 Hz, 1 H, CH_2, **A**), 2.59 (ddd, ^2J = 13.6, ^3J = 8.1, ^3J = 6.4 Hz, 1 H, CH_2, **B**), 2.63 (ddd, ^2J = 13.6, ^3J = 8.1, ^3J = 7.7 Hz, 1 H, CH_2, **B**), 2.81 (ddd, ^2J = 13.9, ^3J = 9.6, ^3J = 5.6 Hz, 1 H, CH_2, **A**), 3.42 (dd, ^3J = 8.1, ^3J = 6.4 Hz, 1 H, C^2H, **B**),

3.67 (dd, ^3J = 9.3, ^3J = 5.6 Hz, 1 H, C^{2}H, **A**), 3.76 (s, 3 H, OCH$_3$, **A**), 3.79 (s, 3 H, OCH$_3$, **B**), 3.81 (s, 6 H, 2 × OCH$_3$, **B**), 3.82 (s, 3 + 3 H, 2 × OCH$_3$, **A**, **B**), 3.82 (s, 6 H, 2 × OCH$_3$, **A**), 5.30 (dd, ^3J = 8.1, ^3J = 7.7 Hz, 1 H, C^{4}H, **B**), 5.33 (dd, ^3J = 9.6, ^3J = 5.8 Hz, 1 H, C^{4}H, **A**), 6.13–6.15 (m, 2 + 2 H, Ar, **A**, **B**).

^{13}C NMR (CDCl$_3$, 150 MHz): δ = 32.66 (C^{2}H), 32.69 (C^{2}H), 34.8 (CH$_2$), 35.1 (CH$_2$), 53.35 (OCH$_3$), 53.39 (OCH$_3$), 53.41 (OCH$_3$), 53.45 (OCH$_3$), 55.2 (2 × OCH$_3$), 55.7 (2 × OCH$_3$+2 × C^{4}H), 90.67 (2 × CH), 90.75 (2 × CH), 103.9 (C), 104.3 (C), 116.0 (2 × CN), 159.6 (2 × C), 159.7 (2 × C), 161.76 (C), 161.83 (C), 166.2 (2 × *C*O$_2$Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_4O_5^+$: 335.1350; found: 335.1350.

Methyl 4-Azido-2-cyano-4-(4-cyanophenyl)butyrate (3n)[4e]

Obtained from 4-cyanobenzaldehyde (3.93 g).

Yield: 3.07 g (38%); dr **A**/**B** 56:44; yellow oil; R_f = 0.26 (PE–EtOAc, 4:1).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 2.18 (ddd, ^2J = 14.2, ^3J = 10.6, ^3J = 3.8 Hz, 1 H, CH$_2$, **A**), 2.30–2.39 (m, 1 + 2 H, CH$_2$, **A**, **B**), 3.61 (dd, ^3J = 7.3, ^3J = 6.1 Hz, 1 H, C^{2}H, **B**), 3.82 (s, 3 H, OCH$_3$, **A**), 3.86 (dd, ^3J = 10.6, ^3J = 4.8 Hz, 1 H, C^{2}H, **A**), 3.88 (s, 3 H, OCH$_3$, **B**), 4.82–4.84 (m, 1 + 1 H, C^{4}H, **A**, **B**), 7.49–7.52 (m, 2 + 2 H, Ar, **A**, **B**), 7.74–7.76 (m, 2 + 2 H, Ar, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(4-nitrophenyl)butyrate (3o)

Obtained from 4-nitrobenzaldehyde (4.53 g).

Yield: 2.41 g (28%); dr **A**/**B** 52:48; yellow oil; R_f = 0.49 (PE–EtOAc, 2:1).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 2.21 (ddd, ^2J = 14.2, ^3J = 10.6, ^3J = 3.9 Hz, 1 H, CH$_2$, **A**), 2.34–2.39 (m, 1 + 2 H, CH$_2$, **A**, **B**), 3.65 (dd, ^3J = 7.3, ^3J = 6.0 Hz, 1 H, C^{2}H, **B**), 3.81 (s, 3 H, OCH$_3$, **A**), 3.87 (s, 3 H, OCH$_3$, **B**), 3.89 (dd, ^3J = 10.6, ^3J = 4.8 Hz, 1 H, C^{2}H, **A**), 4.89–4.91 (m, 1 + 1 H, C^{4}H, **A**, **B**), 7.55–7.60 (m, 2 + 2 H, Ar, **A**, **B**), 8.27–8.30 (m, 2 + 2 H, Ar, **A**, **B**).

^{13}C NMR (CDCl$_3$, 150 MHz): δ = 33.9 (C^{2}H), 34.6 (C^{2}H), 35.7 (CH$_2$), 35.9 (CH$_2$), 53.8 (2 × OCH$_3$), 62.1 (C^{4}H), 62.2 (C^{4}H), 115.4 (2 × CN), 124.38 (2 × CH), 124.42 (2 × CH), 127.8 (2 × CH), 127.9 (2 × CH), 144.6 (C), 144.7 (C), 148.1 (2 × C), 165.4 (*C*O$_2$Me), 165.5 (*C*O$_2$Me)

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}N_5O_4^+$: 290.0884; found: 290.0884.

Methyl 4-Azido-2-cyano-4-(naphthen-1-yl)butyrate (3p)[4e]

Obtained from 1-naphthaldehyde (4.68 g).

Yield: 4.16 g (47%); dr **A**/**B** 53:47; yellow oil; R_f = 0.39 (PE–EtOAc, 4:1).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 2.40 (ddd, ^2J = 14.3, ^3J = 10.7, ^3J = 3.6 Hz, 1 H, CH$_2$, **A**), 2.49–2.57 (m, 1 + 1 H, CH$_2$, **A**, **B**), 2.60 (ddd, ^2J = 14.3, ^3J = 7.7, ^3J = 5.3 Hz, 1 H, CH$_2$, **B**), 3.75 (dd, ^3J = 7.7, ^3J = 5.5 Hz, 1 H, C^{2}H, **B**), 3.80 (s, 3 H, OCH$_3$, **A**), 3.91 (s, 3 H, OCH$_3$, **B**), 3.98 (dd, ^3J = 10.7, ^3J = 4.7 Hz, 1 H, C^{2}H, **A**), 5.55 (dd, ^3J = 9.8, ^3J = 5.3 Hz, 1 H, C^{4}H, **B**), 5.58 (dd, ^3J = 10.6, ^3J = 3.6 Hz, 1 H, C^{4}H, **A**), 7.52–7.64 (m, 4 + 4 H, Ar, **A**, **B**), 7.89–7.92 (m, 1 + 1 H, Ar, **A**, **B**), 7.93–7.96 (m, 1 + 1 H, Ar, **A**, **B**), 8.12 (d, ^3J = 8.4 Hz, 1 H, Ar, **A**), 8.17 (d, ^3J = 8.5 Hz, 1 H, Ar, **B**).

Dimethyl 4,4′-Benzene-1,4-diylbis(4-azido-2-cyanobutyrate) (3q)

Obtained from terephthalaldehyde (4.02 g).

Yield: 6.11 g (50%); dr **A**/**B** 50:50 (for two major isomers); yellow oil; R_f = 0.74 (PE–EtOAc, 1:1).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 2.17–2.23 (m, 1 H, CH$_2$), 2.33–2.42 (m, 3 H, CH$_2$), 3.56–3.59 (m, 1 H, C^{2}H), 3.82 (s, 3 H, OCH$_3$), 3.83–3.86 (m, 1 H, C^{2}H), 3.86 (s, 3 H, OCH$_3$), 4.76–4.81 (m, 2 H, C^{4}H), 7.44–7.46 (m, 4 H, Ar).

^{13}C NMR (CDCl$_3$, 150 MHz): δ = 34.0 (C^{2}H), 34.6 (C^{2}H), 35.5 (CH$_2$), 35.8 (CH$_2$), 53.52 (OCH$_3$), 53.57 (OCH$_3$), 62.3 (C^{4}H), 62.4 (C^{4}H), 115.5 (2 × CN), 127.56 (2 × CH), 127.64 (2 × CH), 138.2 (C), 138.3 (C), 138.4 (C), 138.5 (C), 165.6 (2 × *C*O$_2$Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_8O_4^+$: 411.1524; found: 411.1523.

Methyl (*E*)-4-Azido-2-cyano-6-phenylhex-5-enoate (3r)[4e]

Obtained from *trans*-cinnamaldehyde (3.97 g).

Yield: 3.55 g (44%); dr **A**/**B** 56:44; yellow oil; R_f = 0.62 (PE–EtOAc, 2:1).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 2.17 (ddd, ^2J = 14.0, ^3J = 9.7, ^3J = 4.8 Hz, 1 H, CH$_2$, **A**), 2.22–2.27 (m, 1 + 2 H, CH$_2$, **A**, **B**), 3.68 (dd, ^3J = 7.0, ^3J = 6.8 Hz, 1 H, C^{2}H, **B**), 3.81 (s, 3 H, OCH$_3$, **A**), 3.81 (dd, ^3J = 9.7, ^3J = 5.1 Hz, 1 H, C^{2}H, **A**), 3.86 (s, 3 H, OCH$_3$, **B**), 4.32–4.38 (m, 1 + 1 H, C^{4}H, **A**, **B**), 6.09 (dd, ^3J = 15.7, ^3J = 8.5 Hz, 1 H, CH=, **B**), 6.11 (dd, ^3J = 15.7, ^3J = 8.4 Hz, 1 H, CH=, **A**), 6.76 (d, ^3J = 15.7 Hz, 1 + 1 H, CH=, **A**, **B**), 7.32–7.34 (m, 1 + 1 H, Ar, **A**, **B**), 7.36–7.39 (m, 2 + 2 H, Ar, **A**, **B**), 7.42–7.45 (m, 2 + 2 H, Ar, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(furan-2-yl)butyrate (3s)[4e]

Obtained from furfural (2.88 g).

Yield: 1.91 g (27%); dr **A**/**B** 56:44; brown oil; R_f = 0.67 (PE–EtOAc, 2:1).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 2.34 (ddd, ^2J = 14.1, ^3J = 10.2, ^3J = 4.5 Hz, 1 H, CH$_2$, **A**), 2.50 (ddd, ^2J = 14.1, ^3J = 8.5, ^3J = 6.8 Hz, 1 H, CH$_2$, **B**), 2.50–2.55 (m, 1 H, CH$_2$, **B**), 2.57 (ddd, ^2J = 14.1, ^3J = 10.6, ^3J = 5.1 Hz, 1 H, CH$_2$, **A**), 3.61–3.63 (m, 1 H, C^{2}H, **B**), 3.82 (dd, ^3J = 10.2, ^3J = 5.1 Hz, 1 H, C^{2}H, **A**), 3.84 (s, 3 H, OCH$_3$), 3.87 (s, 3 H, OCH$_3$), 4.77 (dd, ^3J = 8.5, ^3J = 6.8 Hz, 1 H, C^{4}H, **B**), 4.79 (dd, ^3J = 10.6, ^3J = 4.5 Hz, 1 H, C^{4}H, **A**), 6.41–6.42 (m, 1 + 1 H, Fu, **A**, **B**), 6.43–6.44 (m, 1 H, Fu), 6.44–6.45 (m, 1 H, Fu), 7.47–7.48 (m, 1 + 1 H, Fu, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(thien-2-yl)butyrate (3t)[4e]

Obtained from 2-thiophenecarboxaldehyde (3.36 g).

Yield: 3.76 g (50%); dr **A**/**B** 48:52; yellow oil; R_f = 0.46 (pethroleum ether–EtOAc, 2:1).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 2.33 (ddd, ^2J = 14.1, ^3J = 10.0, ^3J = 4.4 Hz, 1 H, CH$_2$, **A**), 2.41–2.49 (m, 2 H, CH$_2$, **B**), 2.50 (ddd, ^2J = 14.1, ^3J = 10.7, ^3J = 5.2 Hz, 1 H, CH$_2$, **A**), 3.67 (dd, ^3J = 7.1, ^3J = 7.0 Hz, 1 H, C^{2}H, **B**), 3.78 (s, 3 H, OCH$_3$, **A**), 3.80 (s, 3 H, OCH$_3$, **B**), 3.89 (dd, ^3J = 10.0, ^3J = 5.2 Hz, 1 H, C^{2}H, **A**), 5.04 (dd, ^3J = 8.7, ^3J = 6.7 Hz, 1 H, C^{4}H, **B**), 5.06 (dd, ^3J = 10.7, ^3J = 4.4 Hz, 1 H, C^{4}H, **A**), 7.02–7.04 (m, 1 + 1 H, Th, **A**, **B**), 7.11–7.15 (m, 1 + 1 H, Th, **A**, **B**), 7.36–7.39 (m, 1 + 1 H, Th, **A**, **B**).

Methyl 4-Azido-2-cyano-4-(1-methyl-1*H*-indol-2-yl)butyrate (3u)

Obtained from 1-methyl-1*H*-indole-2-carbaldehyde (4.78 g).

Yield: 5.18 g (58%); dr **A**/**B** 63:37; brown oil; R_f = 0.63 (PE–EtOAc, 2:1).

^{1}H NMR (CDCl$_3$, 600 MHz): δ = 2.53 (ddd, ^2J = 14.1, ^3J = 9.4, ^3J = 4.7 Hz, 1 H, CH$_2$, **A**), 2.66–2.69 (m, 2 H, CH$_2$, **B**), 2.72 (ddd, ^2J = 14.1, ^3J = 10.3, ^3J = 5.4 Hz, 1 H, CH$_2$, **A**), 3.73–3.75 (m, 1 H, C^{2}H, **B**), 3.80 (s, 3 H, CH$_3$, **A**), 3.82 (s, 3 H, CH$_3$, **B**), 3.83 (s, 3 H, CH$_3$, **A**), 3.88 (s, 3 H, CH$_3$, **B**), 3.91 (dd, ^3J = 9.4, ^3J = 5.4 Hz, 1 H, C^{2}H, **A**), 4.85–4.87 (m, 1 H, C^{4}H, **B**), 4.88 (dd, ^3J = 10.3, ^3J = 4.7 Hz, 1 H, C^{4}H, **A**), 6.60–6.65 (m, 1 + 1 H, Ar, **A**, **B**), 7.17–7.20 (m, 1 + 1 H, Ar, **A**, **B**), 7.31–7.34 (m, 1 + 1 H, Ar, **A**, **B**), 7.37–7.39 (m, 1 + 1 H, Ar, **A**, **B**), 7.65–7.67 (m, 1 + 1 H, Ar, **A**, **B**).

^{13}C NMR (CDCl$_3$, 150 MHz): δ = 29.91 (C^{2}H), 29.94 (C^{2}H), 33.0 (CH$_2$), 33.3 (CH$_2$), 34.4 (NCH$_3$), 34.6 (NCH$_3$), 53.66 (OCH$_3$), 53.73 (OCH$_3$), 55.1 (2 × C^{4}H), 101.5 (CH), 101.7 (CH), 109.3 (CH), 109.4 (CH), 115.4 (CN),

115.5 (CN), 120.07 (CH), 120.11 (CH), 121.00 (CH), 121.03 (CH), 122.74 (CH), 122.79 (CH), 126.7 (2×C), 133.7 (C), 133.9 (C), 138.11 (C), 138.16 (C), 165.56 (CO_2Me), 165.61 (CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N_5O_2^+$: 298.1299; found: 298.1306.

One-Pot Synthesis of 4-Azidobutyronitriles 4

To the **mixture A**, LiCl (1.30 g, 30 mmol) and water (4 mL) were sequentially added. The resulting mixture was heated for 3–6 h at 125 °C, then cooled, diluted with brine (200 mL), and extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with water (3 × 100 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE–EtOAc). Spectral data for azides **4a**, **4e**, and **4f** are consistent with those reported previously.[4e,15]

4-Azido-4-phenylbutyronitrile (4a)[4e]

Obtained from benzaldehyde (3.18 g); reaction time 6 h.

Yield: 2.20 g (39%); yellow oil; R_f = 0.50 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.04 (dddd, ^2J = 13.9, ^3J = 7.7, ^3J = 7.3, ^3J = 5.8 Hz, 1 H, CH_2), 2.12 (dddd, ^2J = 13.9, ^3J = 8.8, ^3J = 7.4, ^3J = 6.2 Hz, 1 H, CH_2), 2.38 (ddd, ^2J = 17.0, ^3J = 7.3, ^3J = 6.2 Hz, 1 H, CH_2), 2.49 (ddd, ^2J = 17.0, ^3J = 7.7, ^3J = 7.4 Hz, 1 H, CH_2), 4.64 (dd, ^3J = 8.8, ^3J = 5.8 Hz, 1 H, CH), 7.32–7.34 (m, 2 H, Ph), 7.38–7.41 (m, 1 H, Ph), 7.42–7.45 (m, 2 H, Ph).

4-Azido-4-(*p*-tolyl)butyronitrile (4b)

Obtained from *p*-tolualdehyde (3.60 g); reaction time 6 h.

Yield 2.67 g (44%); yellow oil; R_f = 0.53 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.02 (dddd, ^2J = 13.9, ^3J = 7.6, ^3J = 7.3, ^3J = 5.9 Hz, 1 H, CH_2), 2.11 (dddd, ^2J = 13.9, ^3J = 8.7, ^3J = 7.4, ^3J = 6.2 Hz, 1 H, CH_2), 2.36 (ddd, ^2J = 17.0, ^3J = 7.3, ^3J = 6.2 Hz, 1 H, CH_2), 2.38 (s, 3 H, CH_3), 2.47 (ddd, ^2J = 17.0, ^3J = 7.6, ^3J = 7.4 Hz, 1 H, CH_2), 4.60 (dd, ^3J = 8.7, ^3J = 5.9 Hz, 1 H, CH), 7.21–7.25 (m, 4 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 14.3 ($^1J_{C–H}$ = 136 Hz, CH_2), 21.1 ($^1J_{C–H}$ = 126 Hz, CH_3), 31.9 ($^1J_{C–H}$ = 133 Hz, CH_2), 64.1 ($^1J_{C–H}$ = 142 Hz, CH), 118.7 (CN), 126.7 (2 × CH), 129.8 (2 × CH), 134.6 (C), 138.9 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}N_4^+$: 201.1135; found: 201.1137.

4-Azido-4-(4-fluorophenyl)butyronitrile (4c)

Obtained from 4-fluorobenzaldehyde (3.72 g); reaction time 3 h.

Yield: 2.56 g (42%); yellow oil; R_f = 0.49 (PE–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.00 (dddd, ^2J = 14.0, ^3J = 7.7, ^3J = 7.2, ^3J = 5.7 Hz, 1 H, CH_2), 2.08 (dddd, ^2J = 14.0, ^3J = 9.0, ^3J = 7.3, ^3J = 6.2 Hz, 1 H, CH_2), 2.38 (ddd, ^2J = 17.0, ^3J = 7.2, ^3J = 6.2 Hz, 1 H, CH_2), 2.49 (ddd, ^2J = 17.0, ^3J = 7.7, ^3J = 7.3 Hz, 1 H, CH_2), 4.63 (dd, ^3J = 9.0, ^3J = 5.7 Hz, 1 H, CH), 7.10–7.14 (m, 2 H, Ar), 7.30–7.34 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 14.2 ($^1J_{C–H}$ = 136 Hz, CH_2), 32.0 ($^1J_{C–H}$ = 133 Hz, CH_2), 63.6 ($^1J_{C–H}$ = 143 Hz, CH), 116.3 ($^2J_{C–F}$ = 22 Hz, 2 × CH), 118.5 (CN), 128.5 ($^3J_{C–F}$ = 8 Hz, 2 × CH), 133.6 ($^4J_{C–F}$ = 3 Hz, C), 162.8 ($^1J_{C–F}$ = 248 Hz, C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}FN_4^+$: 205.0884; found: 205.0887.

4-Azido-4-(4-chlorophenyl)butyronitrile (4d)

Obtained from 4-chlorobenzaldehyde (4.22 g); reaction time 3 h.

Yield: 2.69 g (41%); yellow oil; R_f = 0.61 (PE–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.00 (dddd, ^2J = 14.0, ^3J = 7.8, ^3J = 7.2, ^3J = 5.6 Hz, 1 H, CH_2), 2.08 (dddd, ^2J = 14.0, ^3J = 9.0, ^3J = 7.2, ^3J = 6.2 Hz, 1 H, CH_2), 2.39 (ddd, ^2J = 17.0, ^3J = 7.2, ^3J = 6.2 Hz, 1 H, CH_2), 2.50 (ddd, ^2J = 17.0, ^3J = 7.8, ^3J = 7.2 Hz, 1 H, CH_2), 4.63 (dd, ^3J = 9.0, ^3J = 5.6 Hz, 1 H, CH), 7.27–7.30 (m, 2 H, Ar), 7.40–7.43 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 14.2 ($^1J_{C–H}$ = 136 Hz, CH_2), 31.9 ($^1J_{C–H}$ = 133 Hz, CH_2), 63.6 ($^1J_{C–H}$ = 143 Hz, CH), 118.5 (CN), 128.1 (2 × CH), 129.4 (2 × CH), 134.8 (C), 136.3 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}ClN_4^+$: 221.0589; found: 221.0589.

4-Azido-4-(4-bromophenyl)butyronitrile (4e)[4e]

Obtained from 4-bromobenzaldehyde (5.55 g); reaction time 6 h.

Yield: 2.89 g (36%); orange oil; R_f = 0.62 (PE–EtOAc, 2:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.00 (dddd, ^2J = 14.0, ^3J = 7.8, ^3J = 7.1, ^3J = 5.6 Hz, 1 H, CH_2), 2.07 (dddd, ^2J = 14.0, ^3J = 8.9, ^3J = 7.3, ^3J = 6.1 Hz, 1 H, CH_2), 2.38 (ddd, ^2J = 17.0, ^3J = 7.1, ^3J = 6.1 Hz, 1 H, CH_2), 2.50 (ddd, ^2J = 17.0, ^3J = 7.8, ^3J = 7.3 Hz, 1 H, CH_2), 4.62 (dd, ^3J = 8.9, ^3J = 5.6 Hz, 1 H, CH), 7.22 (br d, ^3J = 8.7 Hz, 2 H, Ar), 7.57 (br d, ^3J = 8.7 Hz, 2 H, Ar).

4-Azido-4-(4-methoxyphenyl)butyronitrile (4f)[15]

Obtained from *p*-anisaldehyde (4.08 g); reaction time 5 h.

Yield: 2.99 g (42%); yellow oil; R_f = 0.56 (PE–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.00 (dddd, ^2J = 13.9, ^3J = 7.5, ^3J = 7.3, ^3J = 6.0 Hz, 1 H, CH_2), 2.10 (dddd, ^2J = 13.9, ^3J = 8.8, ^3J = 7.4, ^3J = 6.3 Hz, 1 H, CH_2), 2.35 (ddd, ^2J = 17.1, ^3J = 7.3, ^3J = 6.3 Hz, 1 H, CH_2), 2.45 (ddd, ^2J = 17.1, ^3J = 7.5, ^3J = 7.4 Hz, 1 H, CH_2), 3.82 (s, 3 H, CH_3O), 4.57 (dd, ^3J = 8.8, ^3J = 6.0 Hz, 1 H, CH), 6.94 (br d, ^3J = 8.8 Hz, 2 H, Ar), 7.25 (br d, ^3J = 8.8 Hz, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 14.2 ($^1J_{C–H}$ = 136 Hz, CH_2), 31.8 ($^1J_{C–H}$ = 133 Hz, CH_2), 55.2 ($^1J_{C–H}$ = 144 Hz, CH_3O), 63.9 ($^1J_{C–H}$ = 142 Hz, CH), 114.4 (2 × CH), 118.7 (CN), 128.0 (2 × CH), 129.5 (C), 159.9 (C).

(5*E*)-4-Azido-6-phenylhex-5-enenitrile (4g)

Obtained from *trans*-cinnamaldehyde (3.96 g); reaction time 3 h.

Yield: 1.40 g (22%); yellow oil; R_f = 0.62 (PE–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.90–1.97 (m, 2 H, CH_2), 2.43–2.53 (m, 2 H, CH_2), 4.21–4.25 (m, 1 H, CH), 6.10 (dd, ^3J = 15.8, ^3J = 8.3 Hz, 1 H, CH=), 6.73 (br d, ^3J = 15.8 Hz, 1 H, CH=), 7.31–7.40 (m, 3 H, Ph), 7.43–7.46 (m, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 13.9 (CH_2), 30.3 (CH_2), 62.9 (CH), 118.7 (CN), 124.6 (CH), 126.7 (2 × CH), 128.5 (CH), 128.7 (2 × CH), 135.0 (CH), 135.2 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_4^+$: 213.1135; found: 213.1137.

4-Azido-4-(thien-2-yl)butyronitrile (4h)

Obtained from 2-thiophenecarboxaldehyde (3.36 g); reaction time 4 h.

Yield: 2.14 g (37%); yellow oil; R_f = 0.62 (PE–EtOAc, 3:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.14 (dddd, ^2J = 13.9, ^3J = 7.7, ^3J = 7.1, ^3J = 6.0 Hz, 1 H, CH_2), 2.18 (dddd, ^2J = 13.9, ^3J = 8.6, ^3J = 7.2, ^3J = 6.3 Hz, 1 H, CH_2), 2.44 (ddd, ^2J = 17.1, ^3J = 7.1, ^3J = 6.3 Hz, 1 H, CH_2), 2.53 (ddd, ^2J = 17.1, ^3J = 7.7, ^3J = 7.2 Hz, 1 H, CH_2), 4.91 (dd, ^3J = 8.6, ^3J = 6.0 Hz, 1 H, CH), 7.05 (dd, ^3J = 5.1, ^3J = 3.5 Hz, 1 H, Th), 7.10 (ddd, ^3J = 3.5, ^4J = 1.2, ^4J = 0.6 Hz, 1 H, Th), 7.37 (ddd, ^3J = 5.1, ^4J = 1.2, ^5J = 0.4 Hz, 1 H, Th).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 14.3 (CH_2), 32.3 (CH_2), 59.5 (CH), 118.4 (CN), 126.3 (CH), 126.4 (CH), 127.0 (CH), 140.3 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_9N_4S^+$: 193.0542; found: 193.0543.

4-Azido-4-(pyridin-3-yl)butyronitrile (4i)

Obtained from 3-pyridinecarboxaldehyde (3.21 g); reaction time 3 h.

Yield: 1.55 g (28%); yellow oil; R_f = 0.60 (EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.02 (dddd, ^2J = 14.0, ^3J = 8.0, ^3J = 7.0, ^3J = 5.3 Hz, 1 H, CH_2), 2.09 (dddd, ^2J = 14.0, ^3J = 9.2, ^3J = 7.2, ^3J = 6.0 Hz, 1 H, CH_2), 2.41 (ddd, ^2J = 17.1, ^3J = 7.0, ^3J = 6.0 Hz, 1 H, CH_2), 2.51 (ddd, ^2J = 17.1, ^3J = 8.0, ^3J = 7.2 Hz, 1 H, CH_2), 4.66 (dd, ^3J = 9.2, ^3J = 5.3 Hz, 1 H, CH), 7.35 (dd, ^3J = 7.9, ^3J = 4.8 Hz, 1 H, Py), 7.64–7.66 (m, 1 H, Py), 8.59 (br d, ^4J = 2.2 Hz, 1 H, Py), 8.62 (dd, ^3J = 4.8, ^4J = 1.6 Hz, 1 H, Py).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 14.2 (CH_2), 31.8 (CH_2), 61.9 (CH), 118.2 (CN), 123.9 (CH), 133.6 (C), 134.1 (CH), 148.3 (CH), 150.4 (CH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{10}N_5^+$: 188.0931; found: 188.0929.

One-Pot Synthesis of 4-Azido-2-cyanobutyramides 5

To **mixture A** (starting from 10.0 mmol of benzaldehyde), the corresponding amine (20.0 mmol) was added in one portion and the resulting mixture was stirred under the specified conditions. The mixture was then diluted with brine (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with water (3 × 100 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE–EtOAc).

4-Azido-*N*-butyl-2-cyano-4-phenylbutyramide (5a)

Obtained from **mixture A** and *n*-butylamine (1.46 g) at r.t.; reaction time 22 h.

Yield: 1.65 g (58%); dr **A**/**B** 55:45; brown oil; R_f = 0.25 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.94 (t, ^3J = 7.4 Hz, 3 H, CH_3, **A**), 0.95 (t, ^3J = 7.4 Hz, 3 H, CH_3, **B**), 1.32–1.40 (m, 2 + 2 H, CH_2, **A**, **B**), 1.49–1.58 (m, 2 + 2 H, CH_2, **A**, **B**), 2.19 (ddd, ^2J = 14.2, ^3J = 10.0, ^3J = 4.3 Hz, 1 H, CH_2, **A**), 2.35 (ddd, ^2J = 14.0, ^3J = 8.9, ^3J = 7.0 Hz, 1 H, CH_2, **B**), 2.42 (ddd, ^2J = 14.0, ^3J = 7.2, ^3J = 6.4 Hz, 1 H, CH_2, **B**), 2.46 (ddd, ^2J = 14.2, ^3J = 10.8, ^3J = 4.9 Hz, 1 H, CH_2, **A**), 2.26–2.34 (m, 2 + 2 H, CH_2, **A**, **B**), 3.39 (dd, ^3J = 7.2, ^3J = 7.0 Hz, 1 H, C^2H, **B**), 3.65 (dd, ^3J = 10.0, ^3J = 4.9 Hz, 1 H, C^2H, **A**), 4.71 (dd, ^3J = 8.9, ^3J = 6.4 Hz, 1 H, C^4H, **B**), 4.74 (dd, ^3J = 10.8, ^3J = 4.3 Hz, 1 H, C^4H, **A**), 6.29 (br s, 1 + 1 H, NH, **A**, **B**), 7.34–7.37 (m, 2 + 2 H, Ph, **A**, **B**), 7.38–7.40 (m, 1 + 1 H, Ph, **A**, **B**), 7.40–7.44 (m, 2 + 2 H, Ph, **A**, **B**).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 13.6 (2 × CH_3), 19.9 (2 × CH_2), 31.2 (2 × CH_2), 35.1 (C^2H), 35.7 (C^2H), 35.9 (CH_2), 36.3 (CH_2), 40.14 (CH_2N), 40.17 (CH_2N), 63.3 (C^4H), 63.4 (C^4H), 117.6 (2 × CN), 126.9 (4 × CH), 129.0 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 137.3 (C), 137.5 (C), 163.47 (CONH), 163.52 (CONH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}N_5O^+$: 286.1662; found: 286.1659.

4-Azido-*N*-benzyl-2-cyano-4-phenylbutyramide (5b)

Obtained from mixture **A** and benzylamine (2.14 g) at 45 °C; reaction time 4 days.

Yield: 1.98 g (31%); dr **A**/**B** 55:45; brown oil; R_f = 0.30 (PE–EtOAc, 4:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.19 (ddd, ^2J = 14.2, ^3J = 10.1, ^3J = 4.2 Hz, 1 H, CH_2, **A**), 2.33 (ddd, ^2J = 14.0, ^3J = 9.0, ^3J = 6.8 Hz, 1 H, CH_2, **B**), 2.38 (ddd, ^2J = 14.0, ^3J = 7.5, ^3J = 6.3 Hz, 1 H, CH_2, **B**), 2.42 (ddd, ^2J = 14.2, ^3J = 10.9, ^3J = 5.0 Hz, 1 H, CH_2, **A**), 3.46 (dd, ^3J = 7.5, ^3J = 6.8 Hz, 1 H, C^2H, **B**), 3.72 (dd, ^3J = 10.1, ^3J = 5.0 Hz, 1 H, C^2H, **A**), 4.38–4.43 (m, 2 H, CH_2N, **A**), 4.41–4.47 (m, 2 H, CH_2N, **B**), 4.64 (dd, ^3J = 9.0, ^3J = 6.3 Hz, 1 H, C^4H, **B**), 4.72 (dd, ^3J = 10.9, ^3J = 4.2 Hz, 1 H, C^4H, **A**), 7.01–7.05 (m, 1 + 1 H, NH, **A**, **B**), 7.26–7.37 (m, 7 + 7 H, Ph, **A**, **B**), 7.38–7.44 (m, 3 + 3 H, Ph, **A**, **B**).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 35.0 (C^2H), 35.6 (C^2H), 35.8 (CH_2), 36.1 (CH_2), 44.07 (CH_2N), 44.10 (CH_2N), 63.1 (2 × C^4H), 117.28 (CN), 117.30 (CN), 126.8 (4 × CH), 127.6 (4 × CH), 127.7 (2 × CH), 128.66 (2 × CH), 128.67 (2 × CH), 128.9 (CH), 128.97 (CH), 128.99 (2 × CH), 129.1 (2 × CH), 136.8 (C), 136.9 (C), 137.2 (C), 137.4 (C), 163.7 (CONH), 163.9 (CONH).

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{18}H_{16}N_5O^-$: 318.1360; found: 318.1361.

4-Azido-4-phenyl-2-(pyrrolidin-1-ylcarbonyl)butyronitrile (5c)

Obtained from the mixture **A** and pyrrolidine (1.42 g) at r.t.; reaction time 26 h.

Yield: 1.03 g (36%); dr **A**/**B** 53:47; yellow oil; R_f = 0.85 (PE–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.87–1.96 (m, 2 + 2 H, CH_2, **A**, **B**), 1.97–2.08 (m, 2 + 2 H, CH_2, **A**, **B**), 2.26 (ddd, ^2J = 13.9, ^3J = 9.5, ^3J = 5.5 Hz, 1 H, CH_2, **B**), 2.28 (ddd, ^2J = 14.2, ^3J = 9.7, ^3J = 4.9 Hz, 1 H, CH_2, **A**), 2.33 (ddd, ^2J = 14.2, ^3J = 10.2, ^3J = 5.7 Hz, 1 H, CH_2, **A**), 2.51 (ddd, ^2J = 13.9, ^3J = 9.1, ^3J = 5.1 Hz, 1 H, CH_2, **B**), 3.39 (ddd, ^2J = 9.8, ^3J = 7.4, ^3J = 6.0 Hz, 1 H, CH_2, **A**), 3.45 (ddd, ^2J = 9.8, ^3J = 7.4, ^3J = 6.0 Hz, 1 H, CH_2, **B**), 3.45–3.57 (m, 2 + 2 H, CH_2, **A**, **B**), 3.59 (dd, ^3J = 9.1, ^3J = 5.5 Hz, 1 H, C^2H, **B**), 3.61–3.66 (m, 1 + 1 H, CH_2, **A**, **B**), 3.70 (dd, ^3J = 9.7, ^3J = 5.7 Hz, 1 H, C^2H, **A**), 4.65 (dd, ^3J = 9.5, ^3J = 5.5 Hz, 1 H, C^4H, **B**), 4.77 (dd, ^3J = 10.2, ^3J = 4.9 Hz, 1 H, C^4H, **A**), 7.33–7.37 (m, 2 + 2 H, Ph, **A**, **B**), 7.38–7.40 (m, 1 + 1 H, Ph, **A**, **B**), 7.40–7.44 (m, 2 + 2 H, Ph, **A**, **B**).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 24.10 (CH_2), 24.12 (CH_2), 25.98 (CH_2), 26.01 (CH_2), 32.4 (C^2H), 33.6 (C^2H), 35.8 (CH_2), 35.9 (CH_2), 46.76 (CH_2), 46.77 (CH_2), 46.82 (2 × CH_2), 63.1 (C^4H), 63.2 (C^4H), 116.5 (CN), 116.6 (CN), 126.79 (2 × CH), 126.81 (2 × CH), 128.95 (CH), 128.99 (CH), 129.1 (4 × CH), 137.7 (C), 137.8 (C), 161.2 (CON), 161.6 (CON).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}N_5O^+$: 284.1506; found: 284.1502.

4-Azido-2-cyano-4-phenylbutyrhydrazide (5d)

Obtained from mixture **A** and hydrazine hydrate (1.00 mL) at r.t.; reaction time 4 h.

Yield: 1.31 g (54%); dr **A**/**B** 54:46; yellow oil; R_f = 0.27 (EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.23 (ddd, ^2J = 14.1, ^3J = 10.1, ^3J = 4.1 Hz, 1 H, CH_2, **A**), 2.34–2.42 (m, 1 + 2 H, CH_2, **A**, **B**), 3.48–3.50 (m, 1 H, C^2H, **B**), 3.73 (dd, ^3J = 10.1, ^3J = 5.0 Hz, 1 H, C^2H, **A**), 4.13 (br s, 2 + 2 H, NH_2, **A**, **B**), 4.66 (dd, ^3J = 8.6, ^3J = 6.5 Hz, 1 H, C^4H, **B**), 4.74 (dd, ^3J = 10.9, ^3J = 4.1 Hz, 1 H, C^4H, **A**), 7.32–7.35 (m, 2 + 2 H, Ph, **A**, **B**), 7.35–7.37 (m, 1 + 1 H, Ph, **A**, **B**), 7.39–7.41 (m, 2 + 2 H, Ph, **A**, **B**). 8.41 (br s, 1 + 1 H, NH, **A**, **B**).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 33.5 (C^2H), 34.1 (C^2H), 35.7 (CH_2), 36.1 (CH_2), 63.05 (C^4H), 63.07 (C^4H), 116.9 (CN), 117.0 (CN), 126.8 (4 × CH), 129.01 (2 × CH), 129.06 (2 × CH), 129.13 (2 × CH), 137.1 (C), 137.3 (C), 164.8 (CONH), 165.0 (CONH).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}N_6O^+$: 245.1145; found: 245.1146.

BF_3-Mediated (3+2)-Cycloaddition within Azides 3 and 4

To a solution of azide **3** or **4** (1.0 mmol) in nitromethane (5 mL) $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol) was added in one portion. The resulting solution was stirred for 10–11 h at 70 °C, then cooled, diluted with brine, and extracted with EtOAc. The combined organic fractions were washed once with water, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE–EtOAc).

$SnCl_4$-Mediated (3+2)-Cycloaddition within Azides 3 and 4

To a solution of azide **3** or **4** (1.0 mmol) in CH_2Cl_2 (10 mL), $SnCl_4$ (1.2 mL of 1 mM solution in CH_2Cl_2, 1.2 mmol) was added slowly by using a syringe. The resulting solution was stirred for 6–24 h (**3**) or 5 d (**4b**) at r.t., then poured into aq $NaHCO_3$ and extracted with EtOAc. The combined organic fractions were washed once with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE–EtOAc).

Methyl 5-Phenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6a)

Obtained from azide **3a** (244 mg).

Yield: 110 mg (45%) ($BF_3{\cdot}OEt_2$); 215 mg (88%) ($SnCl_4$); 210 mg (86%) ($TiCl_4$); yellow oil; dr **A**/**B** = 55:45; R_f = 0.34 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.14 (ddd, ^2J = 13.8, ^3J = 9.1, ^3J = 6.6 Hz, 1 H, C^6H_2), 3.69 (ddd, ^2J = 13.8, ^3J = 7.8, ^3J = 4.1 Hz, 1 H, C^6H_2), 3.841 (s, 3 H, CH_3O), 4.37 (ddd, ^3J = 9.1, ^3J = 4.1, ^4J = 0.6 Hz, 1 H, C^7H), 5.80 (ddd, ^3J = 7.8, ^3J = 6.6, ^4J = 0.6 Hz, 1 H, C^5H), 7.15–7.18 (m, 2 H, Ph), 7.39–7.44 (m, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 37.0 ($^1J_{C–H}$ = 142 Hz, C^7H), 42.8 ($^1J_{C–H}$ = 139 Hz, C^6H_2), 53.3 ($^1J_{C–H}$ = 148 Hz, CH_3O), 60.2 ($^1J_{C–H}$ = 149 Hz, C^5H), 126.1 (2 × CH), 129.17 (CH), 129.22 (2 × CH), 136.2 (C), 160.0 (C), 168.5 (CO_2Me).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.29 (ddd, ^2J = 14.0, ^3J = 6.8, ^3J = 6.7 Hz, 1 H, C^6H_2), 3.70 (ddd, ^2J = 14.0, ^3J = 9.4, ^3J = 8.3 Hz, 1 H, C^6H_2), 3.839 (s, 3 H, CH_3O), 4.32 (dd, ^3J = 9.4, ^3J = 6.8 Hz, 1 H, C^7H), 5.63 (dd, ^3J = 8.3, ^3J = 6.7 Hz, 1 H, C^5H), 7.24–7.26 (m, 2 H, Ph), 7.39–7.44 (m, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 37.0 ($^1J_{C–H}$ = 142 Hz, C^7H), 42.0 ($^1J_{C–H}$ = 139 Hz, C^6H_2), 53.2 ($^1J_{C–H}$ = 148 Hz, CH_3O), 59.9 ($^1J_{C–H}$ = 148 Hz, C^5H), 126.4 (2 × CH), 129.1 (3 × CH), 136.4 (C), 160.0 (C), 168.6 (CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_4O_2^+$: 245.1033; found: 245.1033.

Methyl 5-(*p*-Tolyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6b)

Obtained from azide **3c** (258 mg).

Yield: 122 mg (47%) ($BF_3{\cdot}OEt_2$); 217 mg (84%) ($SnCl_4$); yellow oil; dr **A**/**B** = 52:48; R_f = 0.77 (EtOAc).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.35 (s, 3 H, CH_3), 3.12 (ddd, ^2J = 13.8, ^3J = 9.1, ^3J = 6.7 Hz, 1 H, CH_2), 3.63 (ddd, ^2J = 13.8, ^3J = 7.8, ^3J = 4.0 Hz, 1 H, CH_2), 3.81 (s, 3 H, CH_3O), 4.34 (ddd, ^3J = 9.1, ^3J = 4.0, ^4J = 0.5 Hz, 1 H, CH), 5.72–5.75 (m, 1 H, CH), 7.03–7.06 (m, 2 H, Ar), 7.18–7.21 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 21.1 (CH_3), 37.1 (CH), 42.9 (CH_2), 53.4 (CH_3O), 60.2 (CH), 126.1 (2 × CH), 129.9 (2 × CH), 133.1 (C), 139.33 (C), 159.89 (C), 168.6 (CO_2Me).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.35 (s, 3 H, CH_3), 3.23 (ddd, ^2J = 14.0, ^3J = 6.9, ^3J = 6.7 Hz, 1 H, CH_2), 3.66 (ddd, ^2J = 14.0, ^3J = 9.4, ^3J = 8.3 Hz, 1 H, CH_2), 3.82 (s, 3 H, CH_3O), 4.30 (dd, ^3J = 9.4, ^3J = 6.9 Hz, 1 H, CH), 5.58 (dd, ^3J = 8.3, ^3J = 6.7 Hz, 1 H, CH), 7.11–7.13 (m, 2 H, Ar), 7.18–7.21 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 21.1 (CH_3), 37.0 (CH), 42.0 (CH_2), 53.3 (CH_3O), 59.9 (CH), 126.4 (2 × CH), 129.8 (2 × CH), 133.3 (C), 139.25 (C), 159.85 (C), 168.6 (CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_4O_2^+$: 245.1033; found: 245.1033.

Methyl 5-(4-Fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6c)

Obtained from azide **3d** (262 mg).

Yield: 135 mg (52%) ($BF_3{\cdot}OEt_2$); 240 mg (92%) ($SnCl_4$); beige crystals, mp 151–152 °C; dr **A**/**B** = 54:46; R_f = 0.26 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.12 (ddd, ^2J = 13.9, ^3J = 9.1, ^3J = 6.9 Hz, 1 H, CH_2), 3.66 (ddd, ^2J = 13.9, ^3J = 7.7, ^3J = 3.8 Hz, 1 H, CH_2), 3.81 (s, 3 H, CH_3O), 4.35 (ddd, ^3J = 9.1, ^3J = 3.8, ^4J = 0.5 Hz, 1 H, CH), 5.76–5.79 (m, 1 H, CH), 7.07–7.11 (m, 2 H, Ar), 7.16–7.19 (m, 2 H, Ar).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.22 (ddd, ^2J = 14.0, ^3J = 6.7, ^3J = 6.7 Hz, 1 H, CH_2), 3.70 (ddd, ^2J = 14.0, ^3J = 9.4, ^3J = 8.4 Hz, 1 H, CH_2), 3.82 (s, 3 H, CH_3O), 4.32 (dd, ^3J = 9.4, ^3J = 6.7 Hz, 1 H, CH), 5.64 (dd, ^3J = 8.4, ^3J = 6.7 Hz, 1 H, CH), 7.07–7.11 (m, 2 H, Ar), 7.23–7.26 (m, 2 H, Ar).

Isomers A+B

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.97 (CH), 37.03 (CH), 42.0 (CH_2), 42.9 (CH_2), 53.43 (CH_3O), 53.44 (CH_3O), 59.3 (CH), 59.7 (CH), 116.3 ($^2J_{C–F}$ = 22 Hz, 2 × CH), 116.4 ($^2J_{C–F}$ = 22 Hz, 2 × CH), 128.3 ($^3J_{C–F}$ = 9 Hz, 2 × CH), 128.6 ($^3J_{C–F}$ = 9 Hz, 2 × CH), 131.9 ($^4J_{C–F}$ = 3 Hz, C), 132.2 ($^4J_{C–F}$ = 3 Hz, C), 160.0 (2 × C), 163.9 ($^1J_{C–F}$ = 249 Hz, 2 × C), 168.5 (CO_2Me), 168.6 (CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}FN_4O_2^+$: 263.0939; found: 263.0934.

Methyl 5-(4-Chlorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6d)

Obtained from azide **3e** (279 mg).

Yield: 250 mg (90%) ($SnCl_4$); white crystals, mp 140–141 °C; dr **A**/**B** = 54:46; R_f = 0.37 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.10 (ddd, ^2J = 13.8, ^3J = 9.1, ^3J = 6.8 Hz, 1 H, CH_2), 3.66 (ddd, ^2J = 13.8, ^3J = 7.8, ^3J = 3.8 Hz, 1 H, CH_2), 3.79 (s, 3 H, CH_3O), 4.34 (dd, ^3J = 9.1, ^3J = 3.8 Hz, 1 H, CH), 5.74–5.77 (m, 1 H, CH), 7.11–7.14 (m, 2 H, Ar), 7.34–7.38 (m, 2 H, Ar).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.19 (ddd, ^2J = 14.0, ^3J = 6.7, ^3J = 6.7 Hz, 1 H, CH_2), 3.71 (ddd, ^2J = 14.0, ^3J = 9.5, ^3J = 8.3 Hz, 1 H, CH_2), 3.80 (s, 3 H, CH_3O), 4.32 (dd, ^3J = 9.5, ^3J = 6.7 Hz, 1 H, CH), 5.63 (dd, ^3J = 8.3, ^3J = 6.7 Hz, 1 H, CH), 7.17–7.20 (m, 2 H, Ar), 7.34–7.38 (m, 2 H, Ar).

Isomers A+B

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.9 (CH), 37.0 (CH), 41.9 (CH_2), 42.8 (CH_2), 53.39 (CH_3O), 53.41 (CH_3O), 59.3 (CH), 59.6 (CH), 127.7 (2 × CH), 127.9 (2 × CH), 129.4 (2 × CH), 129.5 (2 × CH), 134.6 (C), 134.9 (C), 135.2 (C), 135.3 (C), 160.0 (2 × C), 168.4 (CO_2Me), 168.5 (CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}ClN_4O_2^+$: 279.0643; found: 279.0641.

Methyl 5-(2-Chlorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6e)

Obtained from azide **3f** (279 mg).

Yield: 258 mg (92%) ($SnCl_4$); colorless oil; dr **A**/**B** = 51:49; R_f = 0.38 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.06 (ddd, ^2J = 13.9, ^3J = 9.3, ^3J = 6.0 Hz, 1 H, CH_2), 3.75 (ddd, ^2J = 13.9, ^3J = 8.3, ^3J = 4.7 Hz, 1 H, CH_2), 3.76 (s, 3 H, CH_3O), 4.30 (ddd, ^3J = 9.3, ^3J = 4.7, ^4J = 0.5 Hz, 1 H, CH), 6.09 (dd, ^3J = 8.3, ^3J = 6.0 Hz, 1 H, CH), 6.73 (br d, ^3J = 7.8 Hz, 1 H, Ar), 7.19–7.23 (m, 1 H, Ar), 7.25–7.30 (m, 1 H, Ar), 7.38–7.41 (m, 1 H, Ar).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.07 (ddd, ^2J = 14.0, ^3J = 6.0, ^3J = 6.0 Hz, 1 H, CH_2), 3.83 (ddd, ^2J = 14.0, ^3J = 9.6, ^3J = 8.6 Hz, 1 H, CH_2), 3.70 (s, 3 H, CH_3O), 4.33 (dd, ^3J = 9.6, ^3J = 6.0 Hz, 1 H, CH), 6.02 (dd, ^3J = 8.6, ^3J = 6.0 Hz, 1 H, CH), 6.79 (br d, ^3J = 7.8 Hz, 1 H, Ar), 7.19–7.23 (m, 1 H, Ar), 7.25–7.30 (m, 1 H, Ar), 7.38–7.41 (m, 1 H, Ar).

Isomers A+B

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.65 (CH), 36.70 (CH), 41.0 (CH_2), 41.3 (CH_2), 53.2 (CH_3O), 53.3 (CH_3O), 57.1 (CH), 57.7 (CH), 126.5 (CH), 126.6 (CH), 127.5 (CH), 127.6 (CH), 129.9 (CH), 130.1 (CH), 130.2 (2 × CH), 132.0 (C), 132.2 (C), 134.1 (C), 134.5 (C), 160.58 (C), 160.64 (C), 168.3 (2 × CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}ClN_4O_2^+$: 279.0643; found: 279.0641.

Methyl 5-(4-Bromophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6f)

Obtained from azide **3g** (323 mg).

Yield: 305 mg (94%) ($SnCl_4$); yellow oil; dr **A**/**B** = 53:47; R_f = 0.30 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.07 (ddd, ^2J = 13.8, ^3J = 9.2, ^3J = 6.9 Hz, 1 H, CH_2), 3.60 (ddd, ^2J = 13.8, ^3J = 7.8, ^3J = 3.8 Hz, 1 H, CH_2), 3.72 (s, 3 H, CH_3O), 4.31 (dd, ^3J = 9.2, ^3J = 3.8 Hz, 1 H, CH), 5.69–5.73 (m, 1 H, CH), 7.02–7.05 (m, 2 H, Ar), 7.43–7.47 (m, 2 H, Ar).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.10 (ddd, ^2J = 14.0, ^3J = 6.6, ^3J = 6.5 Hz, 1 H, CH_2), 3.69 (ddd, ^2J = 14.0, ^3J = 9.5, ^3J = 8.4 Hz, 1 H, CH_2), 3.73 (s, 3 H, CH_3O), 4.29 (dd, ^3J = 9.5, ^3J = 6.6 Hz, 1 H, CH), 5.60 (dd, ^3J = 8.4, ^3J = 6.5 Hz, 1 H, CH), 7.06–7.09 (m, 2 H, Ar), 7.43–7.47 (m, 2 H, Ar).

Isomers A+B

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.79 (CH), 36.83 (CH), 41.7 (CH_2), 42.5 (CH_2), 53.17 (CH_3O), 53.19 (CH_3O), 59.1 (CH), 59.5 (CH), 123.0 (C), 123.1 (C), 127.9 (2 × CH), 128.1 (2 × CH), 132.1 (2 × CH), 132.2 (2 × CH), 135.0 (C), 135.4 (C), 159.9 (C), 160.0 (C), 168.2 (CO_2Me), 168.4 (CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}BrN_4O_2^+$: 323.0138; found: 323.0137.

Methyl 5-(4-Methoxyphenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6g)

Obtained from azide **3h**.

BF_3·OEt_2-Mediated synthesis: **3h** (274 mg, 1.0 mmol); yield 30 mg (14%).

$SnCl_4$-Mediated synthesis: **3h** (97 mg, 0.35 mmol); yield 35 mg (36%).

Yellow oil; dr **A**/**B** = 54:46; R_f = 0.31 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.13 (ddd, ^2J = 13.8, ^3J = 9.0, ^3J = 6.8 Hz, 1 H, CH_2), 3.64 (ddd, ^2J = 13.8, ^3J = 7.7, ^3J = 3.8 Hz, 1 H, CH_2), 3.827 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 4.36 (ddd, ^3J = 9.0, ^3J = 3.8, ^4J = 0.5 Hz, 1 H, CH), 5.74–5.77 (m, 1 H, CH), 6.92–6.96 (m, 2 H, Ar), 7.10–7.13 (m, 2 H, Ar).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.29 (ddd, ^2J = 14.0, ^3J = 6.9, ^3J = 6.7 Hz, 1 H, CH_2), 3.65 (ddd, ^2J = 14.0, ^3J = 9.4, ^3J = 8.3 Hz, 1 H, CH_2), 3.829 (s, 3 H, CH_3O), 3.86 (s, 3 H, CH_3O), 4.30 (dd, ^3J = 9.4, ^3J = 6.9 Hz, 1 H, CH), 5.58 (dd, ^3J = 8.3, ^3J = 6.7 Hz, 1 H, CH), 6.92–6.96 (m, 2 H, Ar), 7.20–7.23 (m, 2 H, Ar).

Isomers A+B

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 37.1 (CH), 37.2 (CH), 42.0 (CH_2), 43.0 (CH_2), 53.5 (2 × CH_3O), 55.39 (CH_3O), 55.40 (CH_3O), 59.8 (CH), 60.1 (CH), 114.7 (2 × CH), 114.8 (2 × CH), 127.7 (2 × CH), 128.0 (C), 128.08 (2 × CH), 128.13 (C), 159.7 (C), 159.8 (C), 160.4 (2 × C), 168.70 (CO_2Me), 168.73 (CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_4O_3^+$: 275.1139; found: 275.1134.

Methyl 5-(3-Methoxyphenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6h)

Obtained from azide **3i** (279 mg).

Yield: 250 mg (90%) ($SnCl_4$); colorless oil; dr **A**/**B** = 54:46; R_f (**A**) = 0.26, R_f (**B**) = 0.18 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.12 (ddd, ^2J = 13.8, ^3J = 9.1, ^3J = 6.6 Hz, 1 H, CH_2), 3.63 (ddd, ^2J = 13.8, ^3J = 7.9, ^3J = 4.2 Hz, 1 H, CH_2), 3.74 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 4.33 (ddd, ^3J = 9.1, ^3J = 4.2, ^4J = 0.5 Hz, 1 H, CH), 5.72 (dd, ^3J = 7.9, ^3J = 6.6 Hz, 1 H, CH), 6.66–6.70 (m, 2 H, Ar), 6.86–6.90 (m, 1 H, Ar), 7.26–7.29 (m, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 37.0 (CH), 42.7 (CH_2), 53.3 (CH_3O), 55.2 (CH_3O), 60.1 (CH), 112.0 (CH), 114.4 (CH), 118.1 (CH), 130.4 (CH), 137.7 (C), 160.0 (C), 160.1 (C), 168.5 (CO_2Me).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.18 (ddd, ^2J = 14.0, ^3J = 6.7, ^3J = 6.5 Hz, 1 H, CH_2), 3.68 (ddd, ^2J = 14.0, ^3J = 9.5, ^3J = 8.4 Hz, 1 H, CH_2), 3.73 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 4.29 (dd, ^3J = 9.5, ^3J = 6.7 Hz, 1 H, CH), 5.58 (dd, ^3J = 8.4, ^3J = 6.5 Hz, 1 H, CH), 6.73–6.78 (m, 2 H, Ar), 6.85–6.88 (m, 1 H, Ar), 7.24–7.28 (m, 1 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.9 (CH), 41.9 (CH_2), 53.2 (CH_3O), 55.1 (CH_3O), 59.8 (CH), 112.1 (CH), 114.5 (CH), 118.5 (CH), 130.2 (CH), 137.9 (C), 160.0 (2 × C), 168.6 (CO_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}ClN_4O_2^+$: 275.1139; found: 275.1137.

Methyl 5-(4-Cyanophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6i)

Obtained from azide **3n** (269 mg).

Yield: 231 mg (86%) ($SnCl_4$); yellow oil; dr **A**/**B** = 49:51; R_f = 0.13 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.11 (ddd, ^2J = 13.9, ^3J = 9.1, ^3J = 6.9 Hz, 1 H, CH_2), 3.70 (ddd, ^2J = 13.9, ^3J = 7.9, ^3J = 3.8 Hz, 1 H, CH_2), 3.76 (s, 3 H, CH_3O), 4.35 (dd, ^3J = 9.1, ^3J = 3.8 Hz, 1 H, CH), 5.83–5.87 (m, 1 H, CH), 7.32–7.34 (m, 2 H, Ar), 7.65–7.68 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.87 (CH), 42.5 (CH_2), 53.34 (CH_3O), 59.5 (CH), 113.1 (C), 117.7 (C), 127.1 (2 × CH), 133.0 (2 × CH), 141.1 (C), 160.3 (C), 168.1 (*C*O_2Me).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.16 (ddd, ^2J = 14.0, ^3J = 6.5, ^3J = 6.4 Hz, 1 H, CH_2), 3.75 (s, 3 H, CH_3O), 3.78 (ddd, ^2J = 14.0, ^3J = 9.4, ^3J = 8.5 Hz, 1 H, CH_2), 4.34 (dd, ^3J = 9.4, ^3J = 6.5 Hz, 1 H, CH), 5.75 (dd, ^3J = 8.5, ^3J = 6.4 Hz, 1 H, CH), 7.35–7.37 (m, 2 H, Ar), 7.65–7.68 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.85 (CH), 41.7 (CH_2), 53.32 (CH_3O), 59.1 (CH), 113.0 (C), 117.8 (C), 127.2 (2 × CH), 132.9 (2 × CH), 141.5 (C), 160.4 (C), 168.3 (*C*O_2Me).

HRMS (ESI): *m*/*z* [M – H]$^+$ calcd for $C_{13}H_{10}N_5O_2^-$: 268.0840; found: 268.0838.

Methyl 5-(4-Nitrophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6j)

Obtained from azide **3o** (289 mg).

Yield: 247 mg (85%) ($SnCl_4$); yellow oil; dr **A**/**B** = 47:53; R_f = 0.17 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.15 (ddd, ^2J = 13.9, ^3J = 9.1, ^3J = 7.0 Hz, 1 H, CH_2), 3.77 (ddd, ^2J = 13.9, ^3J = 7.9, ^3J = 3.7 Hz, 1 H, CH_2), 3.81 (s, 3 H, CH_3O), 4.39 (ddd, ^3J = 9.1, ^3J = 3.7, ^4J = 0.5 Hz, 1 H, CH), 5.91–5.94 (m, 1 H, CH), 7.41–7.43 (m, 2 H, Ar), 8.22–8.26 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 37.0 (CH), 42.7 (CH_2), 53.5 (CH_3O), 59.4 (CH), 124.5 (2 × CH), 127.4 (2 × CH), 143.0 (C), 148.3 (C), 160.37 (C), 168.2 (*C*O_2Me).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.23 (ddd, ^2J = 14.0, ^3J = 6.3, ^3J = 6.2 Hz, 1 H, CH_2), 3.80 (s, 3 H, CH_3O), 3.83 (ddd, ^2J = 14.0, ^3J = 9.5, ^3J = 8.7 Hz, 1 H, CH_2), 4.38 (dd, ^3J = 9.5, ^3J = 6.3 Hz, 1 H, CH), 5.83 (dd, ^3J = 8.6, ^3J = 6.2 Hz, 1 H, CH), 7.44–7.46 (m, 2 H, Ar), 8.22–8.26 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.9 (CH), 41.8 (CH_2), 53.5 (CH_3O), 58.9 (CH), 124.4 (2 × CH), 127.6 (2 × CH), 143.3 (C), 148.2 (C), 160.44 (C), 168.3 (*C*O_2Me).

HRMS (ESI): *m*/*z* [M – H]$^+$ calcd for $C_{12}H_{10}N_5O_4^-$: 288.0738; found: 288.0739.

Methyl 5-(Naphthalen-1-yl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6k)

Obtained from azide **3p** (294 mg).

Yield: 262 mg (89%) ($SnCl_4$); yellow oil; dr **A**/**B** = 53:47; R_f = 0.28 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.12 (ddd, ^2J = 13.7, ^3J = 9.1, ^3J = 5.4 Hz, 1 H, CH_2), 3.88 (ddd, ^2J = 13.7, ^3J = 8.3, ^3J = 5.5 Hz, 1 H, CH_2), 3.80 (s, 3 H, CH_3O), 4.30 (dd, ^3J = 9.0, ^3J = 5.5 Hz, 1 H, CH), 6.51 (dd, ^3J = 8.2, ^3J = 5.4 Hz, 1 H, CH), 6.73–6.76 (m, 1 H, Ar), 7.32–7.37 (m, 1 H, Ar), 7.49–7.58 (m, 2 H, Ar), 7.79–7.85 (m, 2 H, Ar). 7.87–7.90 (m, 1 H, Ar).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.19 (ddd, ^2J = 13.8, ^3J = 5.7, ^3J = 5.6 Hz, 1 H, CH_2), 3.93 (ddd, ^2J = 14.0, ^3J = 9.7, ^3J = 8.5 Hz, 1 H, CH_2), 3.67 (s, 3 H, CH_3O), 4.37 (dd, ^3J = 9.7, ^3J = 5.6 Hz, 1 H, CH), 6.39 (dd, ^3J = 8.5, ^3J = 5.7 Hz, 1 H, CH), 6.90–6.93 (m, 1 H, Ar), 7.32–7.37 (m, 1 H, Ar), 7.49–7.58 (m, 2 H, Ar), 7.79–7.85 (m, 2 H, Ar). 7.87–7.90 (m, 1 H, Ar).

Isomers A+B

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 36.7 (CH), 36.9 (CH), 41.9 (CH_2), 42.2 (CH_2), 53.1 (CH_3O), 53.3 (CH_3O), 57.3 (CH), 57.5 (CH), 121.76 (CH), 121.81 (CH), 122.1 (CH), 122.7 (CH), 125.1 (2 × CH), 126.1 (CH), 126.3 (CH), 127.0 (CH), 127.1 (CH), 129.07 (CH), 129.12 (CH), 129.3 (CH), 129.4 (CH), 129.54 (C), 129.57 (C), 132.3 (C), 132.6 (C), 133.67 (C), 133.74 (C), 160.54 (C), 160.61 (C), 168.37 (*C*O_2Me), 168.40 (*C*O_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_4O_2^+$: 295.1190; found: 295.1187.

Methyl 5-(Thiophen-2-yl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxylate (6l)

Obtained from azide **3t** (250 mg).

Yield: 45 mg (18%) ($SnCl_4$); colorless oil; dr **A**/**B** = 54:46; R_f = 0.25 (PE–EtOAc, 1:1).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.30 (ddd, ^2J = 13.9, ^3J = 8.9, ^3J = 6.4 Hz, 1 H, CH_2), 3.72 (ddd, ^2J = 13.9, ^3J = 7.7, ^3J = 4.3 Hz, 1 H, CH_2), 3.84 (s, 3 H, CH_3O), 4.40 (ddd, ^3J = 8.9, ^3J = 4.3, ^4J = 0.5 Hz, 1 H, CH), 6.06–6.09 (m, 1 H, CH), 7.03–7.05 (m, 1 H, Th), 7.16–7.17 (m, 1 H, Th), 7.38–7.40 (m, 1 H, Th).

Isomer B

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.46 (ddd, ^2J = 14.0, ^3J = 6.4, ^3J = 6.4 Hz, 1 H, CH_2), 3.74 (ddd, ^2J = 14.0, ^3J = 9.4, ^3J = 8.3 Hz, 1 H, CH_2), 3.85 (s, 3 H, CH_3O), 4.32 (dd, ^3J = 9.4, ^3J = 6.4 Hz, 1 H, CH), 5.91 (dd, ^3J = 8.3, ^3J = 6.4 Hz, 1 H, CH), 7.03–7.05 (m, 1 H, Th), 7.20–7.21 (m, 1 H, Th), 7.38–7.40 (m, 1 H, Th).

Isomers A+B

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 37.0 (CH), 37.1 (CH), 41.9 (CH_2), 42.9 (CH_2), 53.50 (CH_3O), 53.53 (CH_3O), 55.5 (CH), 56.0 (CH), 127.0 (CH), 127.2 (CH), 127.4 (CH), 127.48 (CH), 127.51 (CH), 127.6 (CH), 138.0 (C), 138.1 (C), 159.0 (C), 159.1 (C), 168.2 (*C*O_2Me), 168.4 (*C*O_2Me).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}N_4O_2S^+$: 251.0597; found: 251.0596.

***N*-Butyl-5-phenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole-7-carboxamide (6m)**

Obtained from azide **5a** (285 mg).

Yield: 257 mg (90%) ($SnCl_4$); yellow oil; dr **A**/**B** = 56:44. Diastereomers were separated.

trans-**6m**

R_f = 0.39 (PE–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.90 (t, ^3J = 7.4 Hz, 3 H, CH_3), 1.30–1.37 (m, 2 H, CH_2), 1.47–1.53 (m, 2 H, CH_2), 3.08 (ddd, ^2J = 13.7, ^3J = 9.1, ^3J = 6.0 Hz, 1 H, C^6H_2), 3.19–3.25 (m, 1 H, CH_2), 3.30–3.36 (m, 1 H, CH_2),

3.82 (ddd, ^2J = 13.7, ^3J = 8.1, ^3J = 4.5 Hz, 1 H, C^6H_2), 4.28 (dd, ^3J = 9.1, ^3J = 4.5 Hz, 1 H, C^7H), 5.81 (dd, ^3J = 8.1, ^3J = 6.0 Hz, 1 H, C^5H), 7.12 (br s, 1 H, NH), 7.14–7.17 (m, 2 H, Ar), 7.34–7.40 (m, 3 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 13.6 ($^1J_{C-H}$ = 126 Hz, CH_3), 19.9 ($^1J_{C-H}$ = 125 Hz, CH_2), 31.2 ($^1J_{C-H}$ = 126 Hz, CH_2), 37.7 ($^1J_{C-H}$ = 139 Hz, C^7H), 40.0 ($^1J_{C-H}$ = 138 Hz, CH_2), 42.4 ($^1J_{C-H}$ = 139 Hz, C^6H_2), 60.8 ($^1J_{C-H}$ = 151 Hz, C^5H), 126.1 (2 × CH), 129.1 (CH), 129.3 (2 × CH), 136.6 (C), 161.3 (C^8), 166.2 (CO).

cis-**6m**

R_f = 0.23 (PE–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.90 (t, ^3J = 7.4 Hz, 3 H, CH_3), 1.31–1.38 (m, 2 H, CH_2), 1.50–1.55 (m, 2 H, CH_2), 3.24–3.30 (m, 1 H, CH_2), 3.32–3.38 (m, 1 H, CH_2), 3.38 (ddd, ^2J = 14.0, ^3J = 7.1, ^3J = 7.0 Hz, 1 H, C^6H_2), 3.57 (ddd, ^2J = 14.0, ^3J = 9.3, ^3J = 8.4 Hz, 1 H, C^6H_2), 4.20 (dd, ^3J = 9.3, ^3J = 7.1 Hz, 1 H, C^7H), 5.55–5.58 (m, 1 H, C^5H), 7.20 (br s, 1 H, NH), 7.25–7.28 (m, 2 H, Ar), 7.35–7.40 (m, 3 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 13.6 ($^1J_{C-H}$ = 126 Hz, CH_3), 19.9 ($^1J_{C-H}$ = 125 Hz, CH_2), 31.2 ($^1J_{C-H}$ = 126 Hz, CH_2), 37.8 ($^1J_{C-H}$ = 137 Hz, C^7H), 40.0 ($^1J_{C-H}$ = 138 Hz, CH_2), 41.5 ($^1J_{C-H}$ = 139 Hz, C^6H_2), 60.6 ($^1J_{C-H}$ = 149 Hz, C^5H), 126.7 (2 × CH), 129.16 (2 × CH), 129.23 (CH), 136.3 (C), 161.0 (C^8), 166.1 (CO).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}N_5O^+$: 286.1662; found: 286.1661.

5-Phenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole (7a)

Obtained from azide **4a** (372 mg, 2.0 mmol).

Yield: 185 mg (50%) (BF_3·OEt_2); beige crystals, mp 108–109 °C; R_f = 0.71 (EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.82 (dddd, ^2J = 13.5, ^3J = 9.3, ^3J = 6.3, ^3J = 5.9 Hz, 1 H, C^6H_2), 3.05 (ddd, ^2J = 16.9, ^3J = 9.3, ^3J = 6.3 Hz, 1 H, C^7H_2), 3.12 (ddd, ^2J = 16.9, ^3J = 9.3, ^3J = 5.2 Hz, 1 H, C^7H_2), 3.37 (dddd, ^2J = 13.5, ^3J = 9.3, ^3J = 8.2, ^3J = 5.2 Hz, 1 H, C^6H_2), 5.60 (dd, ^3J = 8.2, ^3J = 5.9 Hz, 1 H, C^5H), 7.07–7.11 (m, 2 H, Ph), 7.29–7.35 (m, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 18.4 (C^7H_2), 38.3 (C^6H_2), 60.5 (C^5H), 125.9 (2 × CH), 128.7 (CH), 129.0 (2 × CH), 137.2 (C), 162.5 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}N_4^+$: 187.0978; found: 187.0983.

6-Phenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole (7′a)

Obtained as a side product in the synthesis of **7a**.

Yield: 8 mg (2%); yellow oil; R_f = 0.42 (PE–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.18 (dd, ^2J = 16.8, ^3J = 7.9 Hz, 1 H, C^7H_2), 3.55 (ddd, ^2J = 16.8, ^3J = 8.9, ^4J = 0.7 Hz, 1 H, C^7H_2), 4.35 (dd, ^2J = 11.5, ^3J = 7.8 Hz, 1 H, C^5H_2), 4.50–4.56 (m, 1 H, C^6H).4.80 (ddd, ^2J = 11.5, ^3J = 8.7, ^4J = 0.7 Hz, 1 H, C^5H_2), 7.26–7.28 (m, 2 H, Ph), 7.34–7.43 (m, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 27.9 (C^7H_2), 48.0 (C^6H), 51.8 (C^5H_2), 126.8 (2 × CH), 128.2 (CH), 129.4 (2 × CH), 139.4 (C), 161.5 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}N_4^+$: 187.0978; found: 187.0978.

5-(*p*-Tolyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole (7b)

Obtained from azide **4b** (401 mg, 2.0 mmol).

Yield: 115 mg (29%) (BF_3·OEt_2); 155 mg (39%) ($SnCl_4$); colorless crystals, mp 147–148 °C; R_f = 0.70 (EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.32 (s, 3 H, CH_3), 2.83 (dddd, ^2J = 13.5, ^3J = 9.3, ^3J = 6.2, ^3J = 6.0 Hz, 1 H, CH_2), 3.06 (ddd, ^2J = 16.8, ^3J = 9.2, ^3J = 6.2 Hz, 1 H, CH_2), 3.15 (ddd, ^2J = 16.8, ^3J = 9.3, ^3J = 5.2 Hz, 1 H, CH_2), 3.37 (dddd, ^2J = 13.5, ^3J = 9.2, ^3J = 8.2, ^3J = 5.2 Hz, 1 H, CH_2), 5.58 (dd, ^3J = 8.2, ^3J = 6.0 Hz, 1 H, CH), 6.99–7.03 (m, 2 H, Ar), 7.14–7.18 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 18.5 (CH_2), 21.0 (CH_3), 38.3 (CH_2), 60.5 (CH), 125.9 (2 × CH), 129.7 (2 × CH), 134.2 (C), 138.8 (C), 162.4 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}N_4^+$: 201.1135; found: 201.1136.

5-(4-Fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole (7c)

Obtained from azide **4c** (204 mg).

Yield: 61 mg (30%) (BF_3·OEt_2); beige crystals, mp 123–124 °C; R_f = 0.67 (EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.86 (dddd, ^2J = 13.5, ^3J = 9.3, ^3J = 6.4, ^3J = 6.1 Hz, 1 H, CH_2), 3.12 (ddd, ^2J = 16.8, ^3J = 9.3, ^3J = 6.4 Hz, 1 H, CH_2), 3.20 (ddd, ^2J = 16.9, ^3J = 9.3, ^3J = 5.0 Hz, 1 H, CH_2), 3.42 (dddd, ^2J = 13.5, ^3J = 9.3, ^3J = 8.2, ^3J = 5.0 Hz, 1 H, CH_2), 5.64 (dd, ^3J = 8.2, ^3J = 6.1 Hz, 1 H, CH), 7.06–7.10 (m, 2 H, Ar), 7.13–7.16 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 18.6 (CH_2), 38.5 (CH_2), 60.1 (CH), 116.3 ($^2J_{C-F}$ = 22 Hz, 2 × CH), 128.0 ($^3J_{C-F}$ = 9 Hz, 2 × CH), 133.0 ($^4J_{C-F}$ = 3 Hz, C), 162.5 (C), 162.9 ($^1J_{C-F}$ = 249 Hz, C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}FN_4^+$: 205.0884; found: 205.0883.

5-(4-Methoxyphenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazole (7d)

Obtained from azide **4f** (216 mg).

Yield: 24 mg (11%) (BF_3·OEt_2); yellow oil; R_f = 0.59 (EtOAc).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.85–2.92 (m, 1 H, CH_2), 3.12 (ddd, ^2J = 16.8, ^3J = 9.3, ^3J = 6.3 Hz, 1 H, CH_2), 3.22 (ddd, ^2J = 16.8, ^3J = 9.2, ^3J = 5.1 Hz, 1 H, CH_2), 3.34–3.41 (m, 1 H, CH_2), 3.82 (s, 3 H, CH_3O), 5.58–5.61 (m, 1 H, CH), 6.90–6.93 (m, 2 H, Ar), 7.08–7.11 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 18.7 (CH_2), 38.5 (CH_2), 55.4 (CH_3O), 60.4 (CH), 114.7 (2 × CH), 127.5 (2 × CH), 129.2 (C), 160.1 (C), 162.3 (C).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}N_4O^+$: 217.1084; found: 217.1083.

4-(4-Methoxyphenyl)-4-[5-(4-methoxyphenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*d*]tetrazol-6-yl]butanenitrile (8)

Obtained as the major product in the synthesis of **7d**.

Yield: 70 mg (36%); yellowish crystals, mp 186–187 °C; dr **A**/**B**/**C**/**D** = 69:19:10:3; R_f = 0.76 (EtOAc).

Isomer A

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.71–1.77 (m, 1 H, C^3H_2), 1.98 (ddd, ^2J = 16.4, ^3J = 9.1, ^3J = 7.1 Hz, 1 H, C^2H_2), 2.06–2.11 (m, 1 H, C^3H_2), 2.16 (ddd, ^2J = 16.4, ^3J = 6.8, ^3J = 4.3 Hz, 1 H, C^2H_2), 2.77 (dd, ^2J = 17.0, ^3J = 7.9 Hz, 1 H, C^7H_2), 3.02 (dd, ^2J = 17.0, ^3J = 8.5 Hz, 1 H, C^7H_2), 3.05 (ddd, ^3J = 12.1, ^3J = 9.2, ^3J = 3.4 Hz, 1 H, C^4H), 3.51–3.57 (m, $C^{6'}H$), 3.82 (s, 3 H, CH_3O), 3.84 (s, 3 H, CH_3O), 5.30 (d, ^3J = 7.1 Hz, 1 H, $C^{5'}H$), 6.92–6.94 (m, 2 H, Ar), 6.96–6.98 (m, 2 H, Ar), 7.10–7.12 (m, 2 H, Ar), 7.19–7.21 (m, 2 H, Ar).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 15.2 (C^2H_2), 23.7 ($C^{7'}H_2$), 29.8 (C^3H_2), 47.3 (C^4H), 55.3 (CH_3O), 55.4 (CH_3O), 58.4 ($C^{6'}H$), 65.0 ($C^{5'}H$), 115.0 (4 × CH), 118.8 (CN), 128.2 (C), 128.7 (2 × CH), 129.0 (2 × CH), 129.9 (C), 159.4 (C), 160.0 ($C^{8'}$), 160.5 (C).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{24}N_5O_2^+$: 390.1925; found: 390.1919.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706402.

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