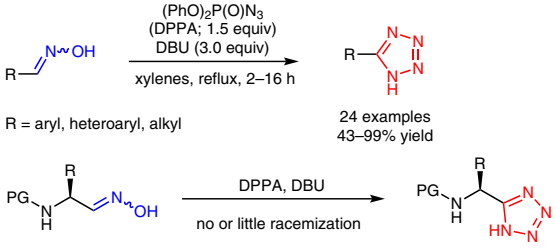
Synthesis K. Ishihara et al. Paper

A Practical Synthesis of 5-Substituted 1*H*-Tetrazoles from Aldoximes Employing the Azide Anion from Diphenyl Phosphorazidate

Kotaro Ishihara[a]
Mayumi Kawashima[a]
Takatoshi Matsumoto[b]
Takayuki Shioiri[a]
Masato Matsugi*[a]

[a] Faculty of Agriculture, Meijo University, 1-501 Shiogamaguchi, Tempaku, Nagoya 468-8502, Japan
matsugi@meijo-u.ac.jp
[b] Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, 2-1-1, Katahira, Aobaku, Sendai 980-8577, Japan



Received: 13.09.2017
Accepted after revision: 07.11.2017
Published online: 12.12.2017
DOI: 10.1055/s-0036-1591851; Art ID: ss-2017-f0595-op

Abstract 5-Substituted 1*H*-tetrazoles were effectively synthesized from aldoximes and diphenyl phosphorazidate (DPPA) under reflux conditions in xylenes. Various aldoximes underwent the cycloaddition reaction to afford the corresponding 5-substituted 1*H*-tetrazoles in short reaction times and in good yields. Chiral aldoximes derived from amino acids also gave aminotetrazoles with almost no racemization.

Keywords diphenyl phosphorazidate, aldoximes, azides, cycloaddition, tetrazoles

Tetrazoles make up an important class of synthetic heterocyclic compounds. Lately, tetrazole components have attracted increasing attention due to their wide range of applications in various areas of science.[1] Especially in medicinal chemistry, tetrazole rings have been utilized as bioisosteres for carboxyl groups owing to their similar properties.[2] Therefore, the tetrazole functionality is found in pharmaceuticals, such as in antihypertensive,[3] antiallergic,[4] antibiotic,[5] antineoplastic,[6] and antiviral agents.[7] They have also been used in agrochemicals,[8] as ligands in coordination chemistry,[9] and in materials science.[10]

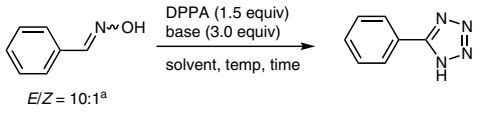
Numerous methods have been developed for the synthesis of tetrazoles;[11–14] 5-substituted 1*H*-tetrazoles have been generally synthesized by the [3+2]-cycloaddition reaction between nitriles and azides in the presence of various catalysts, such as copper (CuI,[15a] CuO,[15b] Cu_2O,[15c] and $CuFe_2O_4$[15d]), iron [$Fe(OAc)_2$[16a] and $FeCl_3$–SiO_2[16b]], zinc ($ZnCl_2$[17a] and $ZnBr_2$[17b–d]), $AlCl_3$;[18] $CdCl_2$,[19] boron compounds [BF_3·OEt_2[20a] and $B(C_6F_5)_3$[20b]], cyanuric chloride,[21] CAN,[22] TABF,[23] $BaWO_4$,[24] $Ln(OTf)_3$–SiO_2,[25] $NaHSO_4$–SiO_2,[26] mesoporous ZnS nanospheres,[27] Zn/Al hydrotalcite,[28] amberlyst-15,[29] COY zeolite,[30] and clay.[31] Methods for the synthesis of 5-substituted 1*H*-tetrazoles from aldoximes or aldehydes in the presence of copper[32] or $InCl_3$[33] catalysts have also been reported. However, some methods have disadvantages such as the need for toxic metals and explosive azide sources.

Recently, we reported the synthesis of 5-substituted 1*H*-tetrazoles from aldoximes by using diphenyl phosphorazidate [DPPA, $(PhO)_2P(O)N_3$].[34,35] This method is safe and environmentally friendly as it does not require toxic metals or explosive azide sources. However, the yields of the desired products were unsatisfactory and longer reaction times were required when sterically hindered substrates were used. Subsequent DFT (B3LYP) calculations indicated that the thermal energy was insufficient to exceed the activation energy barrier in these cases. Increasing the reaction temperature appeared to improve the reactivity. Herein, we report the entire study, including an improvement in the reaction conditions for the rapid synthesis of 5-substituted 1*H*-tetrazoles in good yields, and the application in chiral 1*H*-tetrazole synthesis by using optically active substrates derived from amino acids.

We initially thought to optimize the reaction conditions using benzaldoxime in a model reaction. The reaction conditions were examined by investigating various parameters, including base, solvent, temperature, and reaction time. To investigate the effect of temperature on the reactivity, the reaction was performed at various temperatures and with different solvents (Table 1, entries 1–9). While the desired tetrazole was not obtained at room temperature, the yields improved with increasing reaction temperature in toluene. Elevation of the reaction temperature by using xylenes, which has a higher boiling point, increased the yield and the reaction was complete in four hours. The use of DMF also afforded the desired product in a short time and in a high yield when the reaction temperature was increased, but the use of other solvents with lower boiling points decreased the yields. Other bases were also screened (entries 10–12). The use of pyridine, triethylamine, or *N*,*N*-diisopro-

pylethylamine decreased the yields relative to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Although bis(*p*-nitrophenyl) phosphorazidate (*p*-NO_2DPPA)[36] is more reactive than DPPA in the direct conversion of alcohols into azides, it was unexpectedly less reactive than DPPA in this tetrazole synthesis (entry 13). The yield was scarcely decreased when the quantities of DPPA and DBU were reduced (entry 14). As a result, the reaction proceeded smoothly with DBU in hot xylenes.

Table 1 Optimization of Reaction Conditions



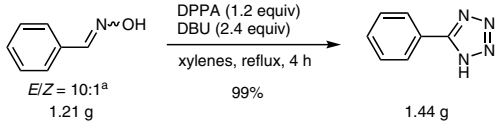
E/*Z* = 10:1[a]

Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	DBU	toluene	r.t.	16	n.d.[b]
2	DBU	toluene	70	16	9
3	DBU	toluene	90	16	43
4	DBU	toluene	110	16	93
5	DBU	xylenes	138–144	4	99
6	DBU	DMF	110	16	70
7	DBU	DMF	140	4	92
8	DBU	THF	66	16	16
9	DBU	MeCN	82	16	30
10	pyridine	xylenes	138–144	4	43
11	Et_3N	xylenes	138–144	4	40
12	DIPEA	xylenes	138–144	4	25
13[c]	DBU	toluene	110	16	56
14[d]	DBU	xylenes	138–144	4	93

[a] *E*/*Z* ratio determined by ^{1}H NMR.
[b] n.d. = not determined.
[c] *p*-NO_2DPPA was used instead of DPPA.
[d] DPPA (1.0 equiv) and DBU (2.0 equiv) were used.

With the optimal reaction conditions in hand, the substrate scope was investigated using various aldoximes in toluene or xylenes, as shown in Table 2. The desired products were not obtained in good yields and a long reaction time was needed when toluene was used, while the use of xylenes afforded the desired products in good yields and in a short reaction time even when inert substrates were used. Aromatic and heteroaromatic aldoximes gave the desired tetrazoles in high yields after short reaction times (entries 1–18). It is noteworthy that the reaction proceeded successfully even for substrates with substituent groups at the *ortho* positions when xylenes are used as solvent (entries 10, 12, 15 and 18). Since it is known that some biologically active compounds have the same skeleton, such as losartan or candesartan,[3] this method can be used to effectively synthesize these compounds (entry 12). Similarly, aliphatic aldoximes afforded improved yields under these conditions (entries 20–24). In particular, a sterically hindered aldoxime dramatically increased the yield (entry 24). Using an aldoxime with a nitro group did not change the yield owing to decomposition of the product (entry 6). Using a substrate containing a cyano group also did not improve the yield, due to formation of a byproduct (entry 13). Vinylic aldoxime did not afford the desired tetrazole in either solvent, because of undesirable side reactions (entry 19).

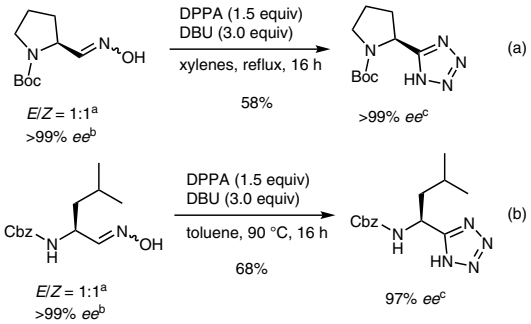
Next, we conducted an experiment to apply this method on gram scale. The substrate was used on gram scale in this reaction to afford the desired product in high yield (Scheme 1).



E/*Z* = 10:1[a] 99% 1.44 g
1.21 g

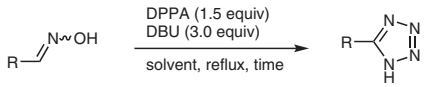
Scheme 1 Gram-scale synthesis of 5-substituted 1*H*-tetrazole. [a] Determined by ^{1}H NMR.

We then demonstrated the application of this method to the synthesis of optically active chiral substrates derived from amino acids and investigated racemization in this reaction. As shown in Scheme 2, both substrates were converted into the corresponding aminotetrazoles in moderate yields. The aldoxime derived from proline was reacted under optimized conditions to give the desired product without loss of enantiomeric purity (Scheme 2, a). The aldoxime derived from leucine afforded the tetrazole with a little racemization. In this case, the reaction was conducted at 90°C in toluene because of decomposition of the product at high temperatures (Scheme 2, b). These tetrazoles were methylated to measure the enantiomeric excess by HPLC.[17c] By employing this method, optically active aldoximes can be converted into the corresponding tetrazoles with no or little racemization. This method would be useful for the synthesis of optically active 1*H*-tetrazoles.



Scheme 2 Application to chiral aldoximes. [a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC. [c] Determined by chiral HPLC of the methylated derivative.

Table 2 Synthesis of 5-Substituted 1*H*-Tetrazoles from Aldoximes



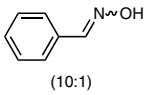
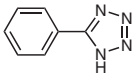
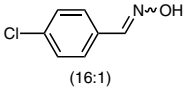
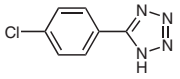
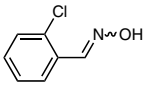
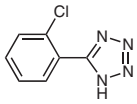
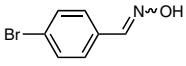
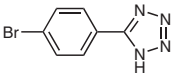
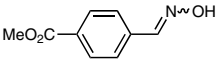
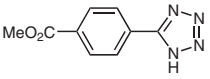
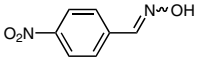
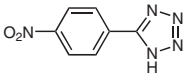
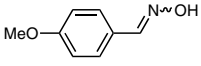
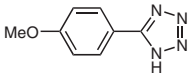
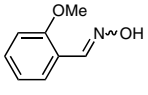
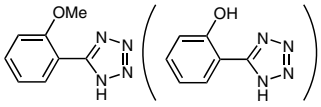
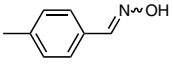
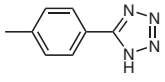
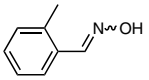
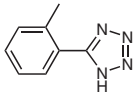
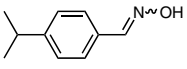
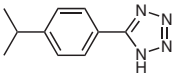
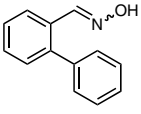
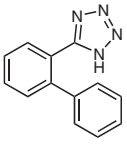
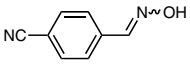
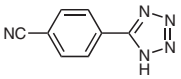
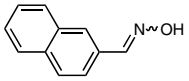
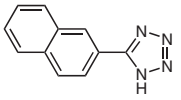
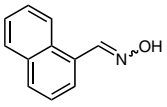
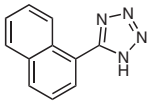
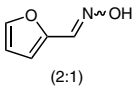
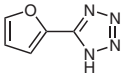
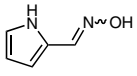
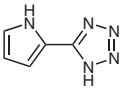
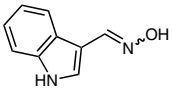
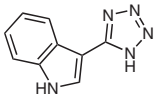
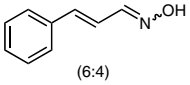
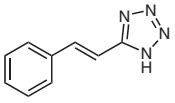
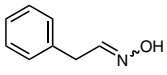
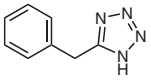
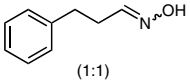
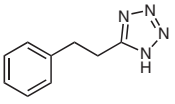
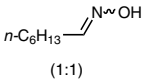
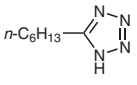
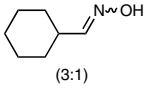
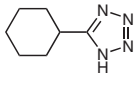
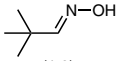
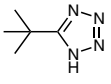
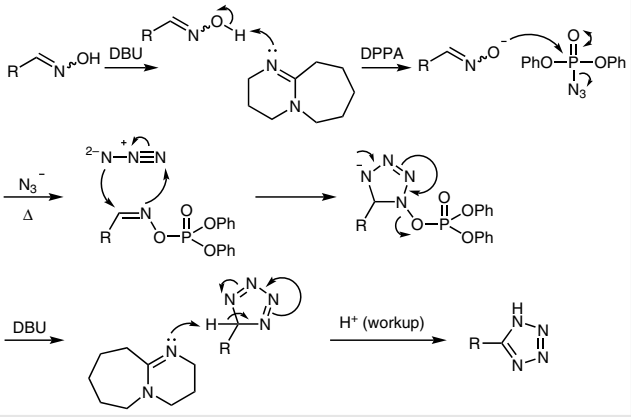
Entry	Substrate (*E*/*Z*)[a]	Product	Toluene		Xylenes	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	 (10:1)		16	93	4	99
2	 (16:1)		16	89	4	99
3	 (10:1)		16	81	4	87
4	 (6:1)		16	81	4	95
5	 (17:1)		16	73	4	88
6	 (10:1)		16	77	2	79
7	 (13:1)		16	81	4	98
8	 (4:1)		16	18[a] (20)[a,b]	4	18[a] (44)[a,b]
9	 (10:1)		16	85	4	94
10	 (7:1)		16	19	16	70
11	 (10:1)		16	80	4	96
12	 (4:1)		16	14	16	77

Table 2 (continued)

Entry	Substrate (*E*/*Z*)[a]	Product	Toluene		Xylenes	
			Time (h)	Yield (%)	Time (h)	Yield (%)
13	 (10:1)		16	38 (20)[c]	4	43 (28)[c]
14	 (3:7)		16	90	4	99
15	 (10:1)		16	51	4	80
16	 (2:1)		16	92	4	98
17	 (5:2)		16	83	4	99
18	 (4:1)		16	35	4	74
19	 (6:4)		16	complex mixture	4	complex mixture
20	 (1:1)		48	71	16	86
21	 (1:1)		48	65	16	83
22	 (1:1)		48	40	16	89
23	 (3:1)		48	33	16	88
24	 (1:0)		16	trace	16	68

[a] Determined by ^{1}H NMR.
[b] Yield of 2-(1*H*-tetrazol-5-yl)phenol shown in parentheses.
[c] Yield of 1,4-di(1*H*-tetrazol-5-yl)benzene shown in parentheses.

A plausible reaction mechanism for this cycloaddition is shown in Scheme 3. The aldoxime is initially deprotonated by DBU and attacks DPPA to form a phosphate intermediate, which activates the C=N bond. The phosphate intermediate is isomerized by heat to assume the *cis* configuration favorable for cycloaddition. Subsequently, cycloaddition of the free azide anion across the C=N bond followed by elimination and tautomerism affords the desired tetrazole. That the free azide anion was generated in situ was confirmed by the reddish-brown color reaction when ferric(III) nitrate was added to the reaction mixture. The phosphate intermediate derived from the aldoxime could not be confirmed owing to its instability. Conversely, the phosphate derived from ketoxime could be isolated. Therefore, it seems that aldoxime would also form the phosphate.



Scheme 3 Plausible reaction mechanism

This reaction presumably does not involve nitrile formation, because the nitrile product was not observed, and this reaction was suppressed when using *p*-NO_2DPPA. If the reaction proceeded via a nitrile, the phosphate intermediate derived from *p*-NO_2DPPA would accelerate the formation of the nitrile intermediate due to its higher elimination ability compared to DPPA phosphate.

In summary, we have achieved an efficient synthesis of 5-substituted 1*H*-tetrazoles by using DPPA and performing the reaction under reflux condition in xylenes. Various aldoximes were easily converted into the corresponding 5-substituted 1*H*-tetrazoles in short times, and good yields were obtained even when sterically hindered substrates were used. Optically active chiral aldoximes derived from amino acids afforded the corresponding aminotetrazoles with no or little racemization. This method is a practical synthetic method that is easy to perform and does not require toxic metals or explosive azide sources.

All the laboratory chemicals were purchased and used without purification unless it is stated otherwise. All reactions were magnetically stirred and monitored by thin-layer chromatography using silica gel plates. Purification by column chromatography was performed on silica gel 60N (spherical, neutral, 63–210 µm, Kanto Chemical Co., Inc.). Melting points were determined in open-ended capillaries using a Bibby Scientific Ltd. Stuart® SMP30 instrument and are uncorrected. All NMR spectra were recorded on a JEOL JNM-EX270 spectrometer. High-resolution mass spectra (HRMS) were measured by EI using JEOL MS-700. High-resolution EI mass spectra were calibrated with PFK. All high-performance liquid chromatography (HPLC) analyses were performed on Hitachi UV L-2140 and L-2400 detectors with a Hitachi L-2130 pump. The chiral HPLC conditions (column, mobile phase, flow rate, and detection wavelength) are indicated in the text.

5-Substituted 1*H*-Tetrazoles; General Procedure

DPPA (0.15 mmol) and DBU (0.30 mmol) were added to a solution of the appropriate aldoxime (0.10 mmol) in xylenes (0.5 mL). After stirring for 2–16 h at reflux, the mixture was cooled to r.t. and sat. aq $NaHCO_3$ (2.0 mL) was added. After stirring for 5 min, the mixture was diluted with water (20 mL). The aqueous layer was then washed with EtOAc (25 mL) and acidified with 1 N aq HCl to pH 2. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with brine (30 mL) and dried over Na_2SO_4. Concentration of the solvent in vacuo followed by purification of the residue on a short column (silica gel, EtOAc–*n*-hexane, 1:1 to 3:1) gave the desired tetrazole.

5-Phenyl-1*H*-tetrazole (Table 2, entry 1)[18b]

Yield: 14.5 mg (99%); white solid; mp 214 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.60–7.66 (m, 3 H), 8.03–8.07 (m, 2 H).

5-(4-Chlorophenyl)-1*H*-tetrazole (Table 2, entry 2)[18b]

Yield: 17.8 mg (99%); white solid; mp 249–250 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.70 (d, *J* = 8.6 Hz, 2 H), 8.06 (d, *J* = 9.2 Hz, 2 H).

5-(2-Chlorophenyl)-1*H*-tetrazole (Table 2, entry 3)[13]

Yield: 15.7 mg (87%); pale yellow solid; mp 170–171 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.57 (t, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 7.6 Hz, 1 H).

5-(4-Bromophenyl)-1*H*-tetrazole (Table 2, entry 4)[18b]

Yield: 21.3 mg (95%); pale yellow solid; mp 257–258 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.84 (d, *J* = 7.3 Hz, 2 H), 7.99 (d, *J* = 6.5 Hz, 2 H).

Methyl 4-(1*H*-Tetrazol-5-yl)benzoate (Table 2, entry 5)[37]

Yield: 18.0 mg (88%); white solid; mp 224–225 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 3.91 (s, 3 H), 8.12 (s, 4 H).

5-(4-Nitrophenyl)-1*H*-tetrazole (Table 2, entry 6)[18b]

Yield: 15.1 mg (79%); yellow solid; mp 216 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.32 (d, *J* = 9.2 Hz, 2 H), 8.47 (d, *J* = 9.2 Hz, 2 H).

5-(4-Methoxyphenyl)-1*H*-tetrazole (Table 2, entry 7)[18b]

Yield: 17.3 mg (98%); white solid; mp 227 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 3.85 (s, 3 H), 7.17 (d, *J* = 8.6 Hz, 2 H), 7.99 (d, *J* = 8.6 Hz, 2 H).

5-(2-Methoxyphenyl)-1*H*-tetrazole[32e] and 2-(1*H*-Tetrazol-5-yl)phenol[13] as mixture (Table 2, entry 8)

5-(2-Methoxyphenyl)-1*H*-tetrazole

Yield: 3.1 mg (18%); white solid.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 3.97 (s, 3 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.59 (t, *J* = 8.1 Hz, 1 H), 8.10 (d, *J* = 5.9 Hz, 1 H).

2-(1*H*-Tetrazol-5-yl)phenol

Yield: 7.1 mg (44%); white solid.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.01 (t, *J* = 7.8 Hz, 1 H), 7.07 (d, *J* = 8.1 Hz, 1 H), 7.41 (t, *J* = 6.9 Hz, 1 H), 7.99 (d, *J* = 5.9 Hz, 1 H).

5-(*p*-Tolyl)-1*H*-tetrazole (Table 2, entry 9)[18b]

Yield: 15.0 mg (94%); white solid; mp 243 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 2.39 (s, 3 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.93 (d, *J* = 7.8 Hz, 2 H).

5-(*o*-Tolyl)-1*H*-tetrazole (Table 2, entry 10)[13]

Yield: 11.2 mg (70%); white solid; mp 150 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 2.49 (s, 3 H), 7.37–7.53 (m, 3 H), 7.69 (d, *J* = 7.8 Hz, 1 H).

5-(4-Isopropylphenyl)-1*H*-tetrazole (Table 2, entry 11)[21]

Yield: 18.0 mg (96%); white solid; mp 189 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.24 (d, *J* = 7.3 Hz, 6 H), 2.93–3.03 (m, 1 H), 7.49 (d, *J* = 7.8 Hz, 2 H), 7.97 (d, *J* = 7.8 Hz, 2 H).

5-([1,1′-Biphenyl]-2-yl)-1*H*-tetrazole (Table 2, entry 12)[38]

Yield: 17.2 mg (77%); white solid; mp 141–142 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.07–7.11 (m, 2 H), 7.29–7.34 (m, 3 H), 7.58 (t, *J* = 7.5 Hz, 2 H), 7.65–7.73 (m, 2 H).

4-(1*H*-Tetrazol-5-yl)benzonitrile (Table 2, entry 13)[31]

Yield: 7.4 mg (43%); white solid; mp 188–189 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 8.10 (d, *J* = 7.8 Hz, 2 H), 8.22 (d, *J* = 8.4 Hz, 2 H).

5-(Naphthalen-2-yl)-1*H*-tetrazole (Table 2, entry 14)[39]

Yield: 19.5 mg (99%); white solid; mp 205 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.62–7.70 (m, 2 H), 8.02–8.18 (m, 4 H), 8.68 (s, 1 H).

5-(Naphthalen-1-yl)-1*H*-tetrazole (Table 2, entry 15)[30]

Yield: 15.7 mg (80%); white solid; mp 210 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.63–7.74 (m, 3 H), 7.99 (d, *J* = 7.3 Hz, 1 H), 8.09 (d, *J* = 9.2 Hz, 1 H), 8.20 (d, *J* = 8.1 Hz, 1 H), 8.55–8.58 (m, 1 H).

5-(Furan-2-yl)-1*H*-tetrazole (Table 2, entry 16)[23]

Yield: 13.4 mg (98%); white solid; mp 202–203 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 6.78–6.80 (m, 1 H), 7.28 (d, *J* = 3.2 Hz, 1 H), 8.05 (d, *J* = 1.9 Hz, 1 H).

5-(1*H*-Pyrrol-2-yl)-1*H*-tetrazole (Table 2, entry 17)[40]

Yield: 13.4 mg (99%); pale gray solid; mp 230 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 6.24–6.27 (m, 1 H), 6.80 (s, 1 H), 7.03 (s, 1 H), 12.02 (br s, 1 H).

3-(1*H*-Tetrazol-5-yl)-1*H*-indole (Table 2, entry 18)[6b]

Yield: 13.7 mg (74%); white solid; mp 229 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 7.20–7.29 (m, 2 H), 7.53–7.56 (m, 1 H), 8.07 (d, *J* = 3.2 Hz, 1 H), 8.20–8.23 (m, 1 H), 11.86 (br s, 1 H).

5-Benzyl-1*H*-tetrazole (Table 2, entry 20)[18b]

Yield: 13.7 mg (86%); white solid; mp 121–122 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 4.29 (s, 2 H), 7.20–7.38 (m, 5 H).

5-Phenethyl-1*H*-tetrazole (Table 2, entry 21)[12]

Yield: 14.5 mg (83%); white solid; mp 97–98 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 3.04 (t, *J* = 7.7 Hz, 2 H), 3.19 (t, *J* = 7.3 Hz, 2 H), 7.16–7.31 (m, 5 H).

5-*n*-Hexyl-1*H*-tetrazole (Table 2, entry 22)[12]

Yield: 13.7 mg (89%); white solid; mp 40–41 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 0.85 (t, *J* = 6.6 Hz, 3 H), 1.24–1.31 (m, 6 H), 1.63–1.72 (m, 2 H), 2.86 (t, *J* = 7.2 Hz, 2 H).

5-Cyclohexyl-1*H*-tetrazole (Table 2, entry 23)[12]

Yield: 13.4 mg (88%); white solid; mp 127–128 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.22–1.58 (m, 5 H), 1.65–1.77 (m, 3 H), 1.98 (t, *J* = 5.9 Hz, 2 H), 2.92–3.03 (m, 1 H).

5-(*tert*-Butyl)-1*H*-tetrazole (Table 2, entry 24)[41]

Yield: 8.6 mg (68%); white solid; mp 206–207 °C.

^{1}H NMR (270 MHz, DMSO-d_6): δ = 1.37 (s, 9 H).

***tert*-Butyl (*S*)-2-(1*H*-Tetrazol-5-yl)pyrrolidine-1-carboxylate (Scheme 2, a)[13]**

DPPA (0.15 mmol) and DBU (0.30 mmol) were added to a solution of *tert*-butyl (*S*)-2-[(hydroxyimino)methyl]pyrrolidine-1-carboxylate (0.10 mmol) in xylenes (0.5 mL). After stirring for 16 h at reflux, the mixture was cooled to r.t. and sat. aq $NaHCO_3$ (2.0 mL) was added. After stirring for 5 min, the mixture was diluted with water (20 mL). The aqueous layer was then washed with EtOAc (25 mL) and acidified with 1.0 N aq HCl to pH 2. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic extracts were washed with brine (30 mL) and dried over Na_2SO_4. Concentration of the solvent in vacuo followed by purification of the residue on a column (silica gel, EtOAc–*n*-hexane, 3:1) gave the desired tetrazole.

Yield: 13.8 mg (58%); white solid; mp 124–125 °C.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.50 (s, 9 H), 2.00–2.18 (m, 2 H), 2.26–2.40 (m, 1 H), 2.94–3.04 (m, 1 H), 3.39–3.44 (m, 2 H), 5.03–5.07 (m, 1 H), 13.43 (br s, 1 H).

***tert*-Butyl (*S*)-2-(1-Methyl-1*H*-tetrazol-5-yl)pyrrolidine-1-carboxylate**

MeI (0.116 mmol) and K_2CO_3 (0.116 mmol) were added to a solution of the tetrazole (0.058 mmol) in DMF (2 mL). After stirring for 16 h at r.t., the mixture was diluted with EtOAc (25 mL). The mixture was washed with sat. aq $NaHCO_3$ and brine (25 mL), and dried over

Na_2SO_4. Concentration of the solvent in vacuo followed by purification of the residue on a column (silica gel, EtOAc–*n*-hexane, 1:1) gave the desired 1-Me isomer (43%) and 2-Me isomer (52%), respectively.

Yield: 6.3 mg (43%); white solid; mp 98–99 °C.

Chiral HPLC: column: Daicel CHIRAL OD-3, 4.6 × 150 mm; solvent: *i*-PrOH–*n*-hexane, 10:90; flow rate: 1.0 mL/min; detector wavelength: 210 nm; retention time (*S*): 7.58 min; >99% ee

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 43.5 Hz, 9 H), 2.00–2.52 (m, 4 H), 3.44–3.64 (m, 2 H), 4.11 (d, *J* = 41.0 Hz, 3 H), 5.07 (d, *J* = 8.1 Hz, 1 H).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{19}N_5O_2$: 253.1539; found: 253.1552.

Benzyl (*S*)-[3-Methyl-1-(1*H*-tetrazol-5-yl)butyl]carbamate (Scheme 2, b)[17d]

DPPA (0.15 mmol) and DBU (0.30 mmol) were added to a solution of benzyl (*S*)-[1-(hydroxyimino)-4-methylpentan-2-yl]carbamate (0.10 mmol) in toluene (0.5 mL). After stirring for 16 h at 90 °C, the mixture was cooled to r.t. and sat. aq $NaHCO_3$ (2.0 mL) was added. After stirring for 5 min, the mixture was diluted with water (20 mL). The aqueous layer was then washed with EtOAc (25 mL) and acidified with 1.0 N aq HCl to pH 2. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic extracts were washed with brine (30 mL) and dried over Na_2SO_4. Concentration of the solvent in vacuo followed by purification of the residue on a column (silica gel, EtOAc–*n*-hexane, 1:1) gave the desired tetrazole.

Yield: 19.6 mg (68%); colorless gummy oil.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.90–0.94 (dd, *J* = 3.2 Hz, 6.2 Hz, 6 H), 1.57–1.72 (m, 1 H), 1.93 (t, *J* = 7.6 Hz, 2 H), 4.99–5.27 (m, 3 H), 6.07 (d, *J* = 8.4 Hz, 1 H), 7.23–7.30 (m, 5 H), 14.92 (br s, 1 H).

Benzyl (*S*)-[3-Methyl-1-(2-methyl-2*H*-tetrazol-5-yl)butyl]carbamate and Benzyl (*S*)-[3-Methyl-1-(1-methyl-1*H*-tetrazol-5-yl)butyl]carbamate Mixture

MeI (0.20 mmol) and K_2CO_3 (0.20 mmol) were added to a solution of the tetrazole (0.10 mmol) in DMF (2 mL). After stirring for 16 h at r.t., the mixture was diluted with EtOAc (30 mL). The mixture was washed with sat. aq $NaHCO_3$ and brine (25 mL), and dried over Na_2SO_4. Concentration of the solvent in vacuo followed by purification of the residue on a column (silica gel, EtOAc–*n*-hexane, 1:2) gave the desired 1-Me and 2-Me isomers as a mixture.

Yield: 29.6 mg (98%); white solid; mp 56–57 °C.

Chiral HPLC: column: Daicel CHIRAL OD-3, 4.6 × 150 mm; solvent: *i*-PrOH–*n*-hexane, 10:90; flow rate: 1.0 mL/min; detector wavelength: 210 nm; retention times (*R*) 9.97 min, (*S*) 11.63 min, (*S*) 12.17 min, and (*R*) 25.19 min; 97% ee.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.96 (dd, *J* = 3.8, 6.5 Hz, 6 H), 1.56–1.70 (m, 1 H), 1.74–1.79 (m, 1 H), 1.84–1.98 (m, 1 H), 4.13 (s, 1.3 H (1-Me)), 4.32 (s, 1.7 H (2-Me)), 5.02–5.26 (m, 4 H), 7.30–7.38 (m, 5 H).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{21}N_5O_2$: 303.1695; found: 303.1684.

Funding Information

This work was supported by JSPS Grant-in-Aid for Scientific Research (C), 26450145, and Prof. Y. Uozumi's JST-ACCEL program (JPMJAC1401).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591851.

References

(1) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 674.
(2) (a) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379. (b) McKie, H. A.; Friedland, S.; Hof, F. *Org. Lett.* **2008**, *10*, 4653.
(3) (a) Chiu, A. T.; Dunica, J. V.; McCall, D. E.; Wong, P. C.; Price, W. A.; Thoolen, M. J.; Carini, D. J.; Johnson, A. L.; Timmermans, P. B. *J. Pharmacol. Exp. Ther.* **1989**, *250*, 867. (b) Buehlmayer, P.; Criscione, L.; Fuhrer, W.; Furet, P.; De Gasparo, M.; Stutz, S.; Whitebread, S. *J. Med. Chem.* **1991**, *34*, 3105. (c) Kinugawa, K.; Kohmoto, O.; Takahashi, T.; Serizawa, T. *Eur. J. Pharmacol.* **1993**, *235*, 313. (d) Shibouta, Y.; Inada, Y.; Ojima, M.; Wada, T.; Noda, M.; Sanada, T.; Kubo, K.; Kohara, Y.; Naka, T.; Nishikawa, K. *J. Pharmacol. Exp. Ther.* **1993**, *266*, 114. (e) Bourdonnec, B. L.; Meulon, E.; Yous, S.; Goossens, J.; Houssin, R.; Hénichart, J. *J. Med. Chem.* **2000**, *43*, 2685. (f) Kurup, A.; Garg, R.; Carini, D. J.; Hansch, C. *Chem. Rev.* **2001**, *101*, 2727. (g) Ostrovskii, V. A.; Trifonov, R. E.; Popova, E. A. *Russ. Chem. Bull.* **2012**, *61*, 768.
(4) (a) Nohara, A.; Kuriki, H.; Saijo, T.; Sugihara, H.; Kanno, M.; Sanno, Y. *J. Med. Chem.* **1977**, *20*, 141. (b) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wrigth, D. E. *J. Med. Chem.* **1986**, *29*, 538. (c) Peet, N. P.; Baugh, L. E.; Sunder, S.; Lewis, J. E.; Matthews, E. H.; Olberding, E. L.; Shah, D. N. *J. Med. Chem.* **1986**, *29*, 2403.
(5) (a) Andrus, A.; Partridge, B.; Heck, J. V.; Christensen, B. G. *Tetrahedron Lett.* **1984**, *25*, 911. (b) Toney, J. H.; Fitzgerald, P. M. D.; Grover-Sharma, N.; Olson, S. H.; May, W. J.; Sundelof, J. G.; Vanderwall, D. E.; Cleary, K. A.; Grant, S. K.; Wu, J. K.; Kozarich, J. W.; Pompliano, D. L.; Hammond, G. G. *Chem. Biol.* **1998**, *5*, 185.
(6) (a) Kumar, C. N. S. S. P.; Parida, D. K.; Santhoshi, A.; Kota, A. K.; Sridhar, B.; Rao, V. J. *MedChemComm* **2011**, *2*, 486. (b) Dolušić, E.; Larrieu, P.; Moineaux, L.; Stroobant, V.; Pilotte, L.; Colau, D.; Pochet, L.; Eynde, B.; Masereel, B.; Wouters, J.; Frédérick, R. *J. Med. Chem.* **2011**, *54*, 5320.
(7) Vieira, E.; Huwyler, J.; Jolidon, S.; Knoflach, F.; Mutel, V.; Wichmann, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4628.
(8) (a) Grayson, B. T.; Webb, J. D.; Deveson, M. R.; Blackman, P. G. *Pestic. Sci.* **1990**, *28*, 123. (b) Sandmann, G.; Schneider, C.; Boger, P. *Z. Naturforsch., C* **1996**, *51*, 534.
(9) (a) Huisgen, R.; Sauer, J.; Sturm, H. J.; Markgraf, J. H. *Chem. Ber.* **1960**, *93*, 2106. (b) Gaponik, P. N.; Voitekhovich, S. V.; Ivashkevich, O. A. *Russ. Chem. Rev.* **2006**, *75*, 507.
(10) (a) Koldobskii, G. L.; Ostrovskii, V. A. *Usp. Khim.* **1994**, *63*, 847. (b) Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. In *Targets in Heterocyclic Systems. Chemistry and Properties*; Attanasi, O. A.; Spinelli, D., Eds.; Italian Society of Chemistry: Camerino, **1999**, 467.
(11) Roh, J.; Vávrová, K.; Hrabálek, A. *Eur. J. Org. Chem.* **2012**, 6101.
(12) Yoneyama, H.; Usami, Y.; Komeda, S.; Harusawa, S. *Synthesis* **2013**, *45*, 1051.
(13) Aureggi, V.; Sedelmeier, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8440.
(14) Treitler, D. S.; Leung, S.; Lindrud, M. *Org. Process Res. Dev.* **2017**, *21*, 460.

(15) (a) Gawande, S. D.; Raihan, M. J.; Zanwar, M. R.; Kavala, V.; Janreddy, D.; Kuo, C.; Chen, M.; Kuo, T.; Yao, C. *Tetrahedron* **2013**, *69*, 1841. (b) Yapuri, U.; Palle, S.; Gudaparthi, O.; Narahari, S. R.; Rawat, D. K.; Mukkanti, K.; Vantikommu, J. *Tetrahedron Lett.* **2013**, *54*, 4732. (c) Jin, T.; Kitahara, F.; Kamjio, S.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 2824. (d) Sreedhar, B.; Suresh Kumar, A.; Yada, D. *Tetrahedron Lett.* **2011**, *52*, 3565.

(16) (a) Bonnamour, J.; Bolm, C. *Chem. Eur. J.* **2009**, *15*, 4543. (b) Nasrollahzadeh, M.; Bayat, Y.; Habibi, D.; Moshaee, S. *Tetrahedron Lett.* **2009**, *50*, 4435.

(17) (a) Vorona, S.; Artamonova, T.; Zevatskii, Y.; Myznikov, L. *Synthesis* **2014**, *46*, 781. (b) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945. (c) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525. (d) Shie, J.; Fang, J. *J. Org. Chem.* **2007**, *72*, 3141.

(18) (a) Matthews, D. P.; Green, J. E.; Shuker, A. J. *J. Comb. Chem.* **2000**, *2*, 19. (b) Nanjundaswamy, H. M.; Abrahamse, H. *Heterocycles* **2014**, *89*, 2137.

(19) Venkateshwarlu, G.; Premalatha, A.; Rajanna, K. C.; Saiprakash, P. K. *Synth. Commun.* **2009**, *39*, 4479.

(20) (a) Kumar, A.; Narayanan, R.; Shechter, H. *J. Org. Chem.* **1996**, *61*, 4462. (b) Prajapti, S. K.; Nagarsenkar, A.; Babu, B. N. *Tetrahedron Lett.* **2014**, *55*, 3507.

(21) Sivaguru, P.; Theerthagiri, P.; Lalitha, A. *Tetrahedron Lett.* **2015**, *56*, 2203.

(22) Kumar, S.; Dubey, S.; Saxena, N.; Awasthi, S. *Tetrahedron Lett.* **2014**, *55*, 6034.

(23) Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccoro, L. *J. Org. Chem.* **2004**, *69*, 2896.

(24) He, J.; Li, B.; Chen, F.; Xu, Z.; Yin, G. *J. Mol. Catal. A: Chem.* **2009**, *304*, 135.

(25) Meshram, G. A.; Deshpande, S. S.; Wagh, P. A.; Vala, V. A. *Tetrahedron Lett.* **2014**, *55*, 3557.

(26) Das, B.; Reddy, C. R.; Kumar, D. N.; Krishnaiah, M.; Narender, R. *Synlett* **2010**, 391.

(27) Lang, L.; Li, B.; Liu, W.; Jiang, L.; Xu, Z.; Yin, G. *Chem. Commun.* **2010**, *46*, 448.

(28) Kantam, M. L.; Shiva Kumar, K. B.; Raja, K. P. *J. Mol. Catal. A: Chem.* **2006**, *247*, 186.

(29) Shelkar, R.; Singh, A.; Nagarkar, J. *Tetrahedron Lett.* **2013**, *54*, 106.

(30) Rama, V.; Kanagaraj, K.; Pitchumani, K. *J. Org. Chem.* **2011**, *76*, 9090.

(31) Chermahini, A. N.; Teimouri, A.; Momenbeik, F.; Zarei, A.; Dalirnasab, Z.; Ghaedi, A.; Roosta, M. *J. Heterocycl. Chem.* **2010**, *47*, 913.

(32) (a) Patil, U. B.; Kumthekar, K. R.; Nagarkar, J. M. *Tetrahedron Lett.* **2012**, *53*, 3706. (b) Akula, R. K.; Adimulam, C. S.; Gangaram, S.; Kengiri, R.; Banda, N.; Pamulaparthy, S. R. *Lett. Org. Chem.* **2014**, *11*, 440. (c) Heravi, M. M.; Fazeli, A.; Oskooie, H. A.; Beheshtiha, Y. S.; Valizadeh, H. *Synlett* **2012**, *23*, 2927. (d) Abdollahi-Alibeik, M.; Moaddeli, A. *New J. Chem.* **2015**, *39*, 2116. (e) Kazemnejadi, M.; Sardarian, A. R. *RSC Adv.* **2016**, *6*, 91999.

(33) Guggilapu, S. D.; Prajapti, S. K.; Nagarsenkar, A.; Gupta, K. K.; Babu, B. N. *Synlett* **2016**, *27*, 1241.

(34) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) For a review, see: Shioiri, T. *TCIMAIL* **2007**, *134*, 2. (c) Shioiri, T. In *New Horizons of Process Chemistry –Scalable Reactions and Technologies*; Tomioka, K.; Shioiri, T.; Sajiki, H., Eds.; Springer Nature: Singapore, **2017**, 131–145.

(35) Ishihara, K.; Kawashima, M.; Shioiri, T.; Matsugi, M. *Synlett* **2016**, *27*, 2225.

(36) (a) For a review, see: Shioiri, T. *Wako Junyaku Jiho* **2005**, *73*, 6. (b) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 855. (c) Mizuno, M.; Shioiri, T. *Chem. Commun.* **1997**, 2165. (d) Ishihara, K.; Hamamoto, H.; Matsugi, M.; Shioiri, T. *Tetrahedron Lett.* **2015**, *56*, 3169.

(37) Tang, H.; Zhang, Z.; Cong, C.; Zhang, K. *Russ. J. Org. Chem.* **2009**, *45*, 559.

(38) Cousaert, N.; Willand, N.; Gesquière, J.; Tartar, A.; Déprez, B.; Deprez-Poulain, R. *Tetrahedron Lett.* **2008**, *49*, 2743.

(39) Zhu, Y.; Ren, Y.; Cai, C. *Helv. Chim. Acta* **2009**, *92*, 171.

(40) Lenda, F.; Guenoun, F.; Tazi, B.; Iarbi, N. B.; Allouchi, H.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2005**, 326.

(41) Behloul, C.; Bouchelouche, K.; Hadji, Y.; Benseghir, S.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis* **2016**, *48*, 2455.