Synthetic Utility of *tert*-Butyl Azidoacetate on the Hemetsberger–Knittel Reaction (Synthetic Studies of Indoles and Related Compounds Part 47)[1)]

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The synthetic utility of *tert*-butyl azidoacetate (7) on the Hemetsberger–Knittel reaction is described. The following two findings are disclosed by using *tert*-butyl azidoacetate (7): i) in the first step for the synthesis of ethyl indole-2-carboxylate 4, the aldol reaction of less reactive aldehydes 1a, b was improved greatly; ii) *tert*-butyl indole-2-carboxylate 10 becomes readily available from aldehydes.

Key word Hemetsberger Knittel–reaction; *tert*-butyl indole-2-carboxylate; *tert*-butyl azidoacetate

The synthesis of functionalized indoles has been of interest to organic chemists for many years due to the large number of biologically active compounds that contain this structural element.[2)] Numerous methods exist to construct the indole skeleton.[3)] Among them, the Hemetsberger–Knittel reaction has been recognized as one of the most important methods for the synthesis of ethyl indole-2-carboxylate **4**, especially that bearing a 4- or 6-substituent.[4)] The indole-2-carboxylate **4** occupies an important position in indole chemistry, perhaps most notably in its service as a masked indole **5**.[5)] Generally, the Hemetsberger–Knittel reaction involves the base-mediated aldol reaction of aryl aldehyde **1** with ethyl azidoacetate (**2**) and subsequent thermal cyclization of 2-azidocinnamate **3**, affording the corresponding indole **4** (Chart 1). But this method has the drawback that **2** tends to decompose under the standard basic reaction conditions and sometimes gives 2-azidocinnamate **3** only in low yield.[4a)]

Recently, we have reported that the aldol reaction at temperatures lower than the previous reactions,[4a,b)] followed by dehydration of the intermediate azidoalcohol **6**, significantly improved the low yield of the azidocinnamate **3** (Chart 2).[6)] However, even under our improved methods, benzaldehyde (**1a**: R=H) and 2-chlorobenzaldehyde (**1b**: R=2-Cl) afforded the azidocinnamate **3a** (R=H), **b** (R=2-Cl) in low to moderate yields.[6)] Due to these facts, we designated **1a** and **1b** as poor aldehydes.

In an effort to ameliorate this problem, we decided to reinvestigate the aldol reaction of **1a** and **1b**. Herein, we would like to describe an improved method for the synthesis of ethyl 2-azidocinnamate **3** using *tert*-butyl azidoacetate (**7**) (Chart 3). During this research, we also found that **7** could be used for the synthesis of *tert*-butyl indole-2-carboxylate **10** (Chart 4). To the best of our knowledge, the Hemetsberger–Knittel reaction with **7** has never been reported.

Aldol Reaction In our previous report,[6)] EtONa/EtOH was the most effective combination for the aldol reaction, as shown in Chart 2. In order to improve the yield of poor substrates **1a, b** mentioned above, we first planned to screen other solvents using EtONa as a base in the aldol reaction of benzaldehyde (**1a**) with ethyl azidoacetate[7)] (**2**). Unfortunately, the use of tetrahydrofuran (THF), diethyl ether, toluene, and *N*,*N*-dimethylformamide in the place of EtOH afforded little or none of the desired product **6a** and/or **3a**. The use of lithium diisopropylamide, *sec*-BuLi, *tert*-BuLi, *tert*-BuOK, and tetrabutylammonium fluoride[8)] (TBAF) as bases in THF, also led to similar disappointing results. We surmised that these poor results might be due to the instability of ethyl azidoacetate (**2**). To circumvent this problem, we investigated the use of the more stable *tert*-butyl azidoacetate[7)] (**7**), which was readily prepared according to the reported manner.[9)] The results are summarized in Table 1. In contrast to the 69% yield obtained with the use of **2** (entry 2), the aldol reaction using **7** was found to proceed with better yield (entry 1). The azidoalcohol[10)] **6a** is probably formed *via* the initial aldol reaction with **7** and subsequent *trans*-esterification of **8a**. In fact, **8a** was detected at the early stage of this aldol reaction (^{1}H-NMR monitor). This procedure was applicable to the reaction of the poorest substrate **1b** (entry 3 *vs.* 4). The much better yield obtained using **7** is especially noteworthy compared with the 38% yield of the reaction using **2** (entry 4). The resulting new procedure allowed the

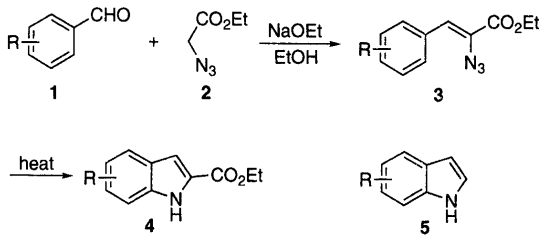
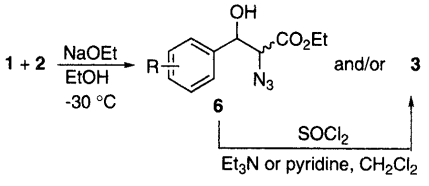


Chart 1. Hemetsberger–Knittel Reaction under the Standard Reaction Conditions



	1, 3, 6, 8, 9	4, 10
a	R = H	R = H
b	2-Cl	4-Cl
c	4-Cl	6-Cl
d	4-MeO	6-MeO
e	4-*tert*-Bu	6-*tert*-Bu
f	2-MeO	4-Meo

Chart 2. Synthesis of Azidocinnamate **3** with Our Improved Methods

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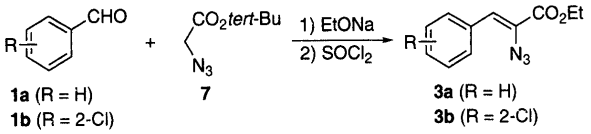


Chart 3. Aldol Reaction of Aldehydes **1a, b** with *tert*-Butylazidoacetate (**7**)

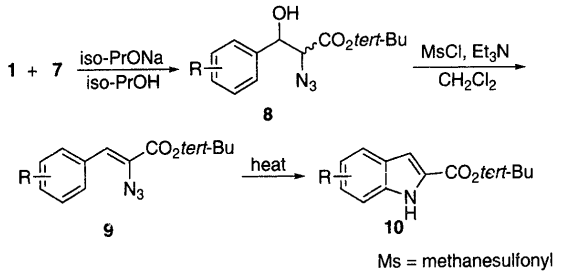


Chart 4. Synthesis of *tert*-Butyl Indole-2-carboxylate **10** with *tert*-Butyl-azidoacetate (**7**)

successful aldol reaction of poor aldehydes **1a, b**. In the case of aldehydes **1c, d**, in which the aldol reaction proceeded with good yields using ethyl azidoacetate (**2**), the choice between **2** and **7** did not appear to be important (Table 2). The *trans*-esterification of the *tert*-butyl ester to ethyl ester under basic conditions is very interesting. Because of the difficulty in separating the stereoisomers, the azidoalcohols[10] **6a—d** were isolated as diastereomeric mixtures. The diastereomeric ratios of **6a—d** were as follows: **6a** (2 : 1), **6b** (2 : 1), **6c** (1 : 1), **6d** (2 : 1), although these relative stereochemistries were not determined. The conversion of **6a—d** and **3a—d** into the indole **4** with good overall yield has been reported.[4a,b]

Synthesis of *tert*-Butyl Indole-2-carboxylate As mentioned above, the *tert*-butyl ester **8a** was detected at the early stage of the aldol reaction. This result prompted us to investigate the synthesis of *tert*-butyl indole-2-carboxylate **10** using *tert*-butyl azidoacetate[7] (**7**). The outline is shown in Chart 4. Accordingly, if sterically bulky iso-PrONa/iso-PrOH could be used for the aldol reaction, the *tert*-butyl ester **8** would be expected to be obtained with good yield. The dehydration of **8**, followed by thermal cyclization of **9**, was then anticipated to give indole **10**. We envisioned that our plan might become a convenient method for the synthesis of **10**.

Using iso-PrONa as a base and iso-PrOH as a solvent, the aldol reaction of aryl aldehyde **1a** with *tert*-butyl azidoacetate (**7**) was examined first. As expected, the desired product **8a** was obtained in 94% yield (entry 1 in Table 3). Using these conditions, a variety of aryl aldehydes **1b—e** were examined and the results obtained are shown in entries 2—6. As can be seen, aldehydes **1b—d** bearing 2- and 4-chloro-, 4-methoxy-, and 4-*tert*-butyl groups gave satisfactory yields (73—97%, entries 2—5). A somewhat lower yield (50%) was observed with **1f** bearing a 2-methoxy group (entry 6). Because of the difficulty in separating the stereoisomers, the azidoalcohols[10] **8a—f** were isolated as diastereomeric mixtures. The diastereomeric ratios of **8a—f** were as follows: **8a** (5 : 1), **8b** (2 : 1), **8c** (4 : 1), **8d** (4 : 1), **8e** (6 : 1), **8f** (3 : 2), although these relative stereochemistries were not determined.

With the azidoalcohols **8a—f** in hand, we turned our attention to their conversion into the indole **10** *via* the dehydration of **8** and the subsequent cyclization of **9**. The dehydration of

Table 1. Aldol Reaction of Poor Aldehydes **1a, b** with **7**[a]

Entry	Aldehyde **1**	Azidoacetate **7** or **2**	Time (h)	Yiled (%)[b] **6**	**3**
1	R= H (**1a**)	**7**	4	84 (**6a**)	7 (**3a**)
2[c]	H (**1a**)	**2**	0.8	69 (**6a**)	0
3	2-Cl (**1b**)	**7**	4	89 (**6b**)	4 (**3b**)
4[c]	2-Cl (**1b**)	**2**	2	38 (**6b**)	0

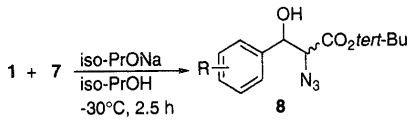
a) Reactions were run with 1 eq of aldehydes **1a, b**, 4 eq of azidoacetate **7**, and 4 eq of NaOEt in EtOH at −30 °C. *b*) Isolated yield. *c*) Previous best results: see ref. 6.

Table 2. Aldol Reaction with Aldehydes **1c, d** with **7**[a]

Entry	Aldehyde **1**	Azidoacetate **7** or **2**	Time (h)	Yield (%)[b] **6**	**3**
1	R= 4-Cl (**1c**)	**7**	4	69 (**6c**)	17 (**3c**)
2[c]	4-Cl (**1c**)	**2**	2.5	74 (**6c**)	12 (**3c**)
3	4-MeO (**1d**)	**7**	4	71 (**6d**)	21 (**3d**)
4[c]	4-MeO (**1d**)	**2**	2.5	70 (**6d**)	28 (**3d**)

a) Reactions were run with 1 eq of aldehydes **1c, d**, 4 eq of azidoacetate **7**, and 4 eq of NaOEt in EtOH at −30 °C. *b*) Isolated yield. *c*) Previous best results: see ref. 6.

Table 3. Aldol Reaction of Aldehyde **1** with **7**[a]



Entry	Aldehyde **1**	Yield (%)[b] of **8**
1	R= H (**1a**)	94 (**8a**)
2	4-Cl (**1c**)	75 (**8c**)
3	4-MeO (**1d**)	73 (**8d**)
4	4-*tert*-Bu (**1e**)	97 (**8e**)
5	2-Cl (**1b**)	81 (**8b**)
6	2-MeO (**1f**)	50 (**8f**)

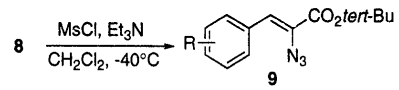
a) 1 eq of aldehyde **1**, 4 eq of azidoacetate **7**, and 4 eq of iso-PrONa were used. *b*) Isolated yield.

8a was first examined with a variety of reagents. After several experiments, the best conditions found were the use of mesyl chloride (MsCl) and Et_3N: and **9a** was obtained in 86% yield (entry 1 in Table 4). Other reagents such as $SOCl_2/Et_3N$, Martin sulfurane dehydration reagent® (bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur),[11] and $K_2S_2O_7$ gave less satisfactory results. Using the best conditions, the dehydration of **8b—f** was examined, as shown in entries 2—6. As can be seen, **8c—e** bearing a 4-substituent gave **9c—e** in good yields (76—85%, entries 2—4). But the results of **8b, f** bearing a 2-substituent, were significantly poor (**8b**: complex mixture, **8f**: 40%, entries 5, 6).[12,13]

Finally, the cyclization of the cinnamates **9a, c—f** was examined, as shown in Table 5. Because aromatic solvents have generally given the best results in the cyclization of **3**, as reported,[4] cyclization reactions were run in *p*-xylene or mesitylene (0.03 M solution of **9**).[14] The indole **10d** bearing a 4-methoxy group was obtained in 78% yield (entry 4), but **10a, c, e, f** were obtained in moderate yields (entries 1—3,5,6).

This overall process is especially useful for the synthesis of 6-substituted *tert*-butyl indole-2-carboxylate[15] **10**. Although these overall yields were moderate, we believe that

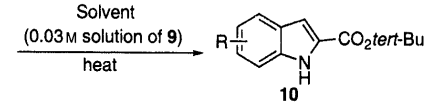
Table 4. Dehydration of **8**[a]



Entry	Azidoalcohol **8**	Yield (%)[b] of **9**
1	R= H (**8a**)	86 (**9a**)
2	4-Cl (**8c**)	85 (**9c**)
3	4-MeO (**8d**)	76 (**9d**)
4	4-*tert*-Bu (**8e**)	81 (**9e**)
5	2-Cl (**8b**)	Complex mixture
6	2-MeO (**8f**)	40 (**9f**)

a) 10 eq of MsCl and 20 eq of Et_3N were used. *b*) Isolated yield.

Table 5. Thermal Cyclization of **9**



Entry	Cinnamate **9**	Solvent	Temp. (°C)	Yield (%)[a] of **10**
1	R= H (**9a**)	Mesitylene	180	45 (**10a**)
2	4-Cl (**9c**)	*p*-Xylene	150	43 (**10c**)
3	4-Cl (**9c**)	Mesitylene	180	53 (**10c**)
4	4-MeO (**9d**)	Mesitylene	150	78 (**10d**)
5	4-*tert*-Bu (**9e**)	Mesitylene	180	54 (**10e**)
6	2-MeO (**9f**)	Mesitylene	180	48 (**10f**)

a) Isolated yield.

the present results will pave the way for further progress. The low yield of the indole **10**, compared with the corresponding ethyl ester **4** in the cyclization, would be caused by decreased reactivity due to steric bulkiness of the *tert*-butyl group and the decomposition of the cinnamate **9** due to a high reaction temperature.

Conclusion

We have succeeded in carrying out the first example of a Hemetsberger–Knittel reaction with the use of *tert*-butyl azidoacetate (**7**), both improving the aldol reaction of poor aldehydes **1a, b**, the first step for the synthesis of ethyl indole-2-carboxylate **4**, and allowing the synthesis of *tert*-butyl indole-2-carboxylate **10**, bearing a 6-substituent.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured on a JASCO FT/IR-230 diffraction grating IR spectrophotometer. ^{1}H-NMR spectra were measured on a JEOL GX-400 NMR spectrometer. All ^{1}H-NMR spectra were reported in δ units, parts per million (ppm) downfield from tetramethylsilane (0 ppm). Electron impact (EI) and FAB-MS were obtained from JEOL JMS-DX-303 and JMS-HX110 instruments, respectively.

tert-Butyl azidoacetate (**7**) was prepared according to the published procedure.[9] All starting aldehydes were commercially available. In general, all reactions were carried out in dry solvents under an argon atmosphere. EtOH was distilled under an argon atmosphere from magnesium/iodine before use. Iso-PrOH and Et_3N were distilled under an argon atmosphere from CaH_2. CH_2Cl_2 was washed with water and brine, then dried over $CaCl_2$, followed by distillation under an argon atmosphere from CaH_2. *p*-Xylene and mesitylene were distilled under an argon atmosphere from sodium. All reagents were available from commercial sources and used without further purification. Silica gel column chromatography was performed on Kanto Chemical Silica gel 60 (spherical, 100—200 μm).

General Procedure for the Aldol Reaction of Aldehyde 1 with *tert*-Butyl Azidoacetate (7) in the Presence of Sodium Ethoxide (Table 1, 2) To a mixture of NaH (60% in mineral oil, 800 mg, 20.0 mmol) and aldehyde **1** (5.00 mmol) in EtOH (15.0 ml), a solution of *tert*-butyl azidoacetate (**7**) (3.14 g, 20.0 mmol) in EtOH (5.0 ml) was gradually added at −30 °C. The whole mixture was stirred for 4 h at the same temperature, quenched by the addition of saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, and concentrated using a rotary evaporator to afford the crude product. Purification by a silica gel column afforded **6** as a more polar fraction and **3** as a less polar fraction. The spectral data of **6a—d** and **3a—d** were identical with those reported (for **6a**: ref. 6, 16. for **6b—d**: ref. 6. for **3a—d**: ref. 4*a*, 6.).

General Procedure for Aldol Reaction of Aldehyde 1 with *tert*-Butyl Azidoacetate (7) in the Presence of Sodium Isopropoxide (Table 3) To a mixture of NaH (60% in mineral oil, 400 mg, 10.0 mmol) and aldehyde **1** (5.00 mmol) in iso-PrOH (25.0 ml), a solution of *tert*-butyl azidoacetate (**7**) (3.14 g, 20.0 mmol) in iso-PrOH (5.0 ml) was gradually added at −30 °C. The whole mixture was stirred for 4 h at the same temperature, quenched by the addition of saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated using a rotary evaporator to afford the crude product. Purification by chromatography on silica gel afforded azidoalcohol **8**. The physical data of all **8a—f** are shown below.

tert-Butyl 2-Azido-3-hydroxy-3-phenylpropionate (**8a**): A colorless viscous oil. *Rf* value=0.24 (EtOAc : benzene=1 : 25). IR (neat) cm^{-1}: 3464 (OH), 2118 (N_3), 1732 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (s, 9H×5/6, $C(CH_3)_3$ of one diastereomer), 1.45 (s, 9H×1/6, $C(CH_3)_3$ of another diastereomer), 2.66 (d, 1H×5/6, *J*=4.9 Hz, OH), 2.98 (d, 1H×1/6, *J*=5.1 Hz, OH), 3.94 (d, 1H×5/6, *J*=4.9 Hz, CHN_3), 4.10 (d, 1H×1/6, *J*=6.8 Hz, CHN_3), 4.98 (dd, 1H×1/6, *J*=6.8, 5.1 Hz, C<u>H</u>OH), 5.12 (dd, 1H×5/6, *J*=4.9, 4.9 Hz, C<u>H</u>OH), 7.31—7.42 (m, 5H, aromatic H). FAB-MS *m/z*: 264 (MH^+). *Anal.* Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.26; H, 6.51; N, 15.81.

tert-Butyl 2-Azido-3-(2-chlorophenyl)-3-hydroxypropionate (**8b**): A pale yellow viscous oil. *Rf* value=0.43 (EtOAc : benzene=1 : 25). IR (neat) cm^{-1}: 3482 (OH), 2116 (N_3), 1733 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (s, 9H×1/3, $C(CH_3)_3$ of one diastereomer), 1.43 (s, 9H×2/3, $C(CH_3)_3$ of another diastereomer), 2.79—2.96 (br, 1H×2/3, OH), 3.15—3.31 (br, 1H×1/3, OH), 4.02 (d, 1H×2/3, *J*=3.0 Hz, CHN_3), 4.08 (d, 1H×1/3, *J*=5.0 Hz, CHN_3), 5.27—5.31 (br, 1H×1/3, C<u>H</u>OH), 5.50—5.56 (br, 1H×2/3, C<u>H</u>OH), 7.16—7.28 (m, 4H×2/3, aromatic H), 7.46—7.58 (m, 4H×1/3, aromatic H). EI-MS *m/z*: 300 (MH^++2), 298 (MH^+), 218, 216, 57 (bp). *Anal.* Calcd for $C_{13}H_{16}N_3O_3Cl$: C, 52.44; H, 5.42; N, 14.11. Found: C, 52.51; H, 5.25; N, 14.14.

tert-Butyl 2-Azido-3-(4-chlorophenyl)-3-hydroxypropionate (**8c**): A pale yellow oil. *Rf* value=0.32 (EtOAc : benzene=1 : 25). IR (neat) cm^{-1}: 3464 (OH), 2116 (N_3), 1732 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (s, 9H×4/5, $C(CH_3)_3$ of one diastereomer), 1.36 (s, 9H×1/5, $C(CH_3)_3$ of another diastereomer), 2.90 (br s, 1H×4/5, OH), 3.16 (br s, 1H×1/5, *J*=5.0 Hz, OH), 3.79 (d, 1H×4/5, *J*=4.0 Hz, CHN_3), 3.88 (d, 1H×1/5, *J*=6.0 Hz, CHN_3), 4.83 (dd, 1H×1/5, *J*=6.0, 4.0 Hz, C<u>H</u>OH), 5.00 (dd, 1H×4/5, *J*=5.0, 4.0 Hz, C<u>H</u>OH), 7.19—7.21 (m, 4H, aromatic H). FAB-MS *m/z*: 300 (MH^++2), 298 (MH^+). *Anal.* Calcd for $C_{13}H_{16}N_3O_3Cl$: C, 52.44; H, 5.42; N, 14.11. Found: C, 52.44; H, 5.39; N, 14.01.

tert-Butyl 2-Azido-3-hydroxy-3-(4-methoxyphenyl)propionate (**8d**): A pale yellow oil. *Rf* value=0.33 (EtOAc : benzene=1 : 25). IR (neat) cm^{-1}: 3456 (OH), 2113 (N_3), 1731 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (s, 9H×4/5, $C(CH_3)_3$ of one diastereomer), 1.47 (s, 9H×1/5, $C(CH_3)_3$ of another diastereomer), 2.58 (br s, 1H×4/5, OH), 2.88 (br s, 1H×1/5, OH), 3.81 (s, 3H, OCH_3), 3.90 (d, 1H×4/5, *J*=5.1 Hz, CHN_3), 3.98 (d, 1H×1/5, *J*=7.0 Hz, CHN_3), 4.92 (d, 1H×1/5, *J*=7.0 Hz, C<u>H</u>OH), 5.06 (d, 1H×4/5, *J*=5.1 Hz, C<u>H</u>OH), 6.90 (d, 2H, *J*=8.7 Hz, aromatic H), 7.32 (d, 2H, *J*=8.7 Hz, aromatic H). EI-MS *m/z*: 293 (M^+), 265, 137 (bp), 57. *Anal.* Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.00; H, 6.69; N, 13.94.

tert-Butyl 2-Azido-3-(4-*tert*-butylphenyl)-3-hydroxypropionate (**8e**): Colorless needles (benzene–hexane), mp 71—72 °C. *Rf* value=0.22 (EtOAc : benzene=1 : 25). IR (KBr) cm^{-1}: 3507 (OH), 2123 (N_3), 1711 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (s, 9H×6/7, $C(CH_3)_3$ of one diastereomer), 1.33 (s, 9H×6/7, $C(CH_3)_3$ of one diastereomer), 1.38 (s, 9H×1/7, $C(CH_3)_3$ of another diastereomer), 1.50 (s, 9H×1/7, $C(CH_3)_3$ of another diastereomer), 2.48 (d, 1H×6/7, *J*=4.5 Hz, OH), 2.79 (d, 1H×1/7, *J*=4.5 Hz, OH), 3.86 (d, 1H×6/7, *J*=5.0 Hz, CHN_3), 3.92 (d, 1H×1/7, *J*=6.5 Hz, CHN_3), 4.89 (dd,

1H×1/7, J=6.5, 4.5 Hz, CHOH), 5.01 (dd, 1H×6/7, J=5.0, 4.5 Hz, CHOH), 7.22—7.34 (m, 4H, aromatic H). FAB-MS *m/z*: 320 (MH^+). *Anal.* Calcd for $C_{17}H_{25}N_3O_3$: C, 63.93; H, 7.89; N, 13.16. Found: C, 63.95; H, 8.13; N, 12.96.

tert-Butyl 2-Azido-3-hydroxy-3-(2-methoxyphenyl)propionate (**8f**): A pale yellow viscous oil. *Rf* value=0.33 (EtOAc : benzene=1 : 25). IR (neat) cm^{-1}: 3494 (OH), 2112 (N_3), 1733 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 9H×2/5, $C(CH_3)_3$ of one diastereomer), 1.46 (s, 9H×3/5, $C(CH_3)_3$ of another diastereomer), 3.03 (d, 1H×3/5, J=6.5 Hz, OH), 3.37 (d, 1H×2/5, J=7.0 Hz, OH), 3.89 (s, 3H, 1H×3/5, OCH_3), 3.90 (s, 3H, 1H×2/5, OCH_3), 4.13 (d, 1H×2/5, J=6.0 Hz, CHN_3), 4.18 (d, 1H×3/5, J=4.5 Hz, CHN_3), 5.18 (dd, 1H×2/5, J=7.0, 6.0 Hz, CHOH), 5.37 (dd, 1H×3/5, J=6.5, 4.5 Hz, CHOH), 6.90—7.05, 7.31—7.44 (m, 4H, aromatic H). FAB-MS *m/z*: 294 (MH^+). *Anal.* Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.13; H, 6.55; N, 14.16.

General Procedure for the Dehydration of *tert*-Butyl 2-Azido-3-hydroxy-3-(substituted phenyl)propionate 8, as Shown in Table 4 To a stirred solution of **8** (4.5 mmol) in CH_2Cl_2 (17.0 ml) were added dropwise Et_3N (12.5 ml, 90.0 mmol) and MsCl (3.5 ml, 45.0 mol) at −40 °C. The reaction mixture was stirred for 10 min at the same temperature, then quenched by the addition of saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated using a rotary evaporator to afford the crude product. Purification by chromatography on silica gel afforded azidocinnamate **9**. The physical data of **9a**, **c**—**f** are shown below.

tert-Butyl 2-Azidocinnamate (**9a**): A pale yellow viscous oil. *Rf* value=0.28 (benzene : hexane=1 : 4). IR (neat) cm^{-1}: 2117 (N_3), 1708 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.66 (s, 9H, $C(CH_3)_3$), 6.91 (s, 1H, CH=), 7.37—7.47 (m, 3H, aromatic H), 7.86 (d, 1H, J=7.0 Hz, aromatic H). EI-MS *m/z*: 245 (M^+), 217, 85 (bp), 57. *Anal.* Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C,63.27; H, 5.99; N, 17.55.

tert-Butyl 2-Azido-4′-chlorocinnamate (**9c**): A pale yellow viscous oil. *Rf* value=0.35 (benzene : hexane=1 : 4). IR (neat) cm^{-1}: 2116 (N_3), 1712 (C=O). 1H-NMR ($CDCl_3$) δ: 1.59 (s, 9H, $C(CH_3)_3$), 6.76 (s, 1H, CH=), 7.34 (d, 2H, J=8.0 Hz, aromatic H), 7.74 (d, 1H, J=8.0 Hz, aromatic H). EI-MS *m/z*: 281 (M^++2), 279 (M^+), 208, 206, 152, 150 (bp), 57. *Anal.* Calcd for $C_{13}H_{14}N_3O_2Cl$: C, 55.82; H, 5.04; N, 15.02. Found: C, 56.00; H, 4.82; N,14.89.

tert-Butyl 2-Azido-4′-methoxycinnamate (**9d**): A pale yellow viscous oil. *Rf* value=0.15 (benzene : hexane=1 : 4). IR (KBr) cm^{-1}: 2112 (N_3), 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.51 (s, 9H, $C(CH_3)_3$), 3.75 (s, 3H, OCH_3), 6.73 (s, 1H, CH=), 6.82 (d, 2H, J=8.8 Hz, aromatic H), 7.72 (d, 1H, J=8.8 Hz, aromatic H). EI-MS *m/z*: 275 (M^+), 247, 146, 83, 57 (bp). *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.46; H, 6.31; N, 14.94.

tert-Butyl 2-Azido-4′-*tert*-butylcinnamate (**9e**): A pale yellow viscous oil. *Rf* value=0.33 (benzene : hexane=1 : 4). IR (KBr) cm^{-1}: 2114 (N_3), 1712 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 9H, aryl $C(CH_3)_3$), 1.59 (s, 9H, $CO_2C(CH_3)_3$), 6.83 (s, 1H, CH=), 7.39 (d, 2H, J=8.0 Hz, aromatic H), 7.73 (d, 1H, J=8.0 Hz, aromatic H). EI-MS *m/z*: 301 (M^+), 273, 83, 57(bp). *Anal.* Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.64; H, 7.90; N, 13.75.

tert-Butyl 2-Azido-2′-methoxycinnamate (**9f**): A pale yellow viscous oil. *Rf* value=0.08 (benzene : hexane=1 : 4). IR (KBr) cm^{-1}: 2105 (N_3), 1702 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.59 (s, 9H, $C(CH_3)_3$), 3.85 (s, 3H, OCH_3), 6.88 (dd, 1H, J=7.9, 1.0 Hz, aromatic H), 6.98 (dd, 1H, J=7.9, 7.9 Hz, aromatic H), 7.27—7.36 (m, 1H, aromatic H), 7.32 (br s, 1H, CH=), 8.15 (dd, 1H, J=7.9, 2.0 Hz, aromatic H). EI-MS *m/z*: 275 (M^+), 247, 202, 147, 83 (bp), 57. *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N,15.26. Found: C, 61.45; H, 6.33; N, 14.90.

General Procedure for the Cyclization of *tert*-Butyl 2-Azido-3-(substituted phenyl)propionate 9, as Shown in Table 5 To mesitylene (20.0 ml) was gradually added a solution of **9** (0.840 mmol) in mesitylene (5.0 ml) under reflux. After stirring for 5 min, the reaction mixture was allowed to cool and was then concentrated using a rotary evaporator to afford the crude product. Purification by chromatography on silica gel afforded indole **10**. The physical data of **10a**—**f** are shown below.

tert-Butyl Indole-2-carboxylate (**10a**): Colorless needles (benzene–hexane), mp 109—110 °C. *Rf* value=0.18 (benzene : hexane=1 : 1). IR (KBr) cm^{-1}: 3355 (NH), 1685 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.62 (s, 9H, $C(CH_3)_3$), 7.11—7.15 (m, 2H, C3, C5 or C6-H), 7.30 (ddd, 1H, J=8.0, 6.5, 1.0 Hz, C5 or C6-H), 7.41 (ddd, 1H, J=8.0, 2.5, 1.0 Hz, C4-H), 7.68 (ddd, 1H, J=8.0, 2.5, 1.0 Hz, C7-H), 8.92 (br s, 1H, NH). FAB-MS *m/z*: 217 (MH^+). *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.63; H, 7.20; N, 6.15.

tert-Butyl 6-Chloroindole-2-carboxylate (**10c**): Colorless needles (benzene–hexane), mp 143—145 °C. *Rf* value=0.24 (benzene : hexane=1 : 1). IR (KBr) cm^{-1}: 3327 (NH), 1684 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.62 (s, 9H, $C(CH_3)_3$), 7.09—7.12 (m, 2H, C3 and C4-H), 7.41 (br s, 1H, C7-H), 7.57 (br d, 1H, J=8.0 Hz, C5-H), 8.96 (br s, 1H, NH). EI-MS *m/z*: 253 (M^++2), 251 (M^+), 197, 195, 179, 177 (bp), 151, 149, 57. *Anal.* Calcd for $C_{13}H_{14}NO_2Cl$: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.29; H, 5.68; N, 5.50.

tert-Butyl 6-Methoxyindole-2-carboxylate (**10d**): Colorless needles (benzene–hexane), mp 153—155 °C. *Rf* value=0.24 (benzene). IR (KBr) cm^{-1}: 3329 (NH), 1679 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.61 (s, 9H, $C(CH_3)_3$), 3.85 (s, 3H, OCH_3), 6.80 (dd, 1H, J=8.0, 2.0 Hz, C4 or C5-H), 6.84 (br s, 1H, C3 or C7-H), 7.08 (dd, 1H, J=2.0, 1.0 Hz, C3 or C7-H), 7.52 (br d, 1H, J=8.0 Hz, C4 or C5-H), 8.89 (br s, 1H, NH). EI-MS *m/z*: 247 (M^+), 191 (bp), 149, 57. *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.90; H, 6.97; N, 5.60.

tert-Butyl 6-*tert*-Butylindole-2-carboxylate (**10e**): Colorless plates (benzene–hexane), mp 182—183 °C. *Rf* value=0.26 (benzene : hexane=1 : 1). IR (KBr) cm^{-1}: 3334 (NH), 1679 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (s, 9H, aryl $C(CH_3)_3$), 1.68 (s, 9H, $CO_2C(CH_3)_3$), 7.10 (dd, 1H, J=2.0, 1.0 Hz, C3-H), 7.23 (dd, 1H, J=8.0, 2.0 Hz, C4-H), 7.41 (dd, 1H, J=1.0, 1.0 Hz, C7-H), 7.60 (br d, 1H, J=8.0 Hz, C5-H), 8.97 (br s, 1H, NH). EI-MS *m/z*: 273 (M^+, bp), 218, 119, 57. *Anal.* Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.56; H, 8.60; N, 5.13.

tert-Butyl 4-Methoxyindole-2-carboxylate (**10f**): Colorless needles (benzene–hexane), mp 177—179 °C. *Rf* value=0.29 (benzene). IR (KBr) cm^{-1}: 3325 (NH), 1695 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.57 (s, 9H, $C(CH_3)_3$), 3.91 (s, 3H, OCH_3), 6.45 (d, 1H, J=8.0 Hz, C5 or C7-H), 6.95 (d, 1H, J =8.0 Hz, C5 or C7-H), 7.17 (dd, 1H, J=8.0, 8.0 Hz, C6-H), 7.21 (br s, 1H, C3-H), 8.94 (br s, 1H, NH). EI-MS *m/z*: 247 (M^+), 192 (bp), 119, 57. *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.96; H, 6.99; N, 5.64.

References and Notes

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7) Crude **2** and **7** were used without purification in all aldol reactions, as they were quantitatively prepared from the corresponding haloacetates.
8) We have already reported that TBAF was usable for the aldol reaction of aryl aldehyde **1** and ethyl azidoacetate **2**. See ref. 6.
9) Moore A. T., Rydon H. N., *Org. Synth.*, **45**, 47—49 (1965).
10) In general, β-azidoalcohol could be converted into β-aminoalcohol, which is a useful building block. See: *a*) Shin C., Yonezawa Y., Unoki K., Yoshimura J., *Bull. Chem. Soc. Jpn*, **52**, 1657—1660 (1979); *b*) Lampe J. W., Hughes P. F., Biggers C. K., Smith S. H., Hu H., *J. Org. Chem.*, **59**, 5147—5148 (1994); *c*) Hughes P. F., Smith S. H., Olson J. T., *ibid.*, **59**, 5799—5802 (1994), and references cited therein.
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12) The use of $SOCl_2$/Et_3N also gave poor results.
13) The geometry of the (*Z*)-olefin in **9** was judged from the fact that a single isomer of **9** (judged by ^{1}H-NMR) obtained by the dehydration

of **8** was converted into **10**, as the direct judgement of the geometry by ^{1}H-NMR was impossible.

14) A dilute solution of **9** in mesitylene was crucial for this efficient cyclization.

15) In general, syntheses of *tert*-butyl indole-2-carboxylate derivatives **10** reported so far involve the conversion of an ethyl ester into a *tert*-butyl ester *via* the hydrolysis of **4** and subsequent *tert*-butylation of **11**, as shown in Chart 5. For example, see: Unangst P. C., Connor D. T., Miller S. R., *J. Heterocyclic Chem.*, **33**, 1627—1630 (1996).

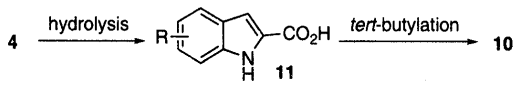

Chart 5

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