Microwave-Assisted Regiospecific Synthesis of Pseudohalohydrin Esters

Mirna El Khatib,[a] Mohamed Elagawany,[a,b,c] Ekaterina Todadze,[a] Levan Khelashvili,[a] Said A. El-Feky,[b] Alan R. Katritzky*[a,d]

[a] Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA
E-mail: katritzky@chem.ufl.edu

[b] Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig 44519, Egypt

[c] Department of Organic Chemistry, College of Pharmacy, Misr University for Science and Technology, Al-Motamayez District, P.O. Box 77, 6th of October City, Egypt

[d] Department of Chemistry, King Abdulaziz University, Jeddah 21589, Saudi Arabia

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Abstract: *N*-Acylbenzotriazoles react regiospecifically with epoxides under palladium catalysis to give novel β-(benzotriazol-1-yl)ethyl esters (52–87%) constituting halohydrin ester surrogates.

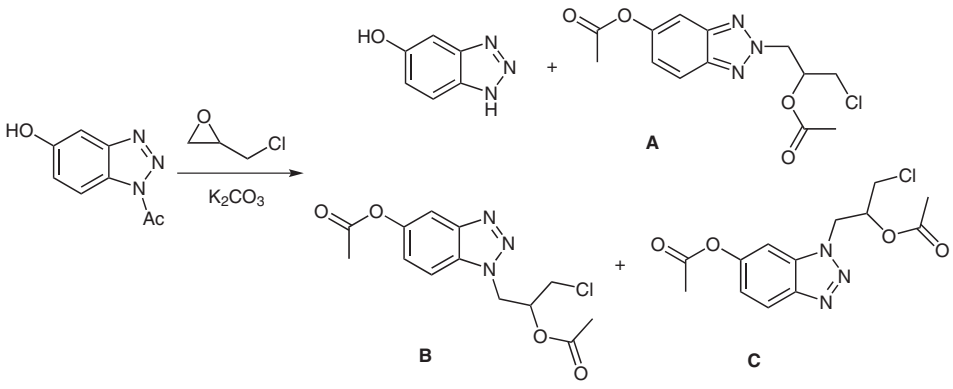
Key words: regioselectivity, catalysis, palladium, esters, ring opening

Halohydrin esters are important intermediates in asymmetric syntheses of a wide range of biologically active natural and synthetic products[1–6] including drugs,[7] β-amino alcohols,[8] pyrrolidines,[9] and functionalized cyclopropanes.[10]

Halohydrin esters[11–13] are commonly prepared by (i) direct reaction of an epoxide with an acyl halide,[1,4,5,12,13] (ii) the ring-opening of epoxides by halogen nucleophiles followed by the O-acylation of the resulting halohydrin derivatives,[14–19] and (iii) from 1,2-diols.[6,20] In general, these strategies produce mixtures of regioisomers and side products. No previous general method has achieved the high regioselectivity which we now report.

N-Acylbenzotriazoles, which are more stable than acid chlorides and have advantageously replaced them in many acylations, often reducing side reactions.[21,22] N-Acylbenzotriazoles have thus enabled advantageous Friedel–Crafts and Vilsmeier–Haack acylations.[21,23] Obase et al.[24] previously synthesized a pseudohalohydrin ester (Scheme 1) from an *N*-acylbenzotriazole. However, the single example reported gave a mixture of three products, the parent benzotriazole, and two isomeric pseudohalohydrin esters **A** and **B**. The structures of **A** (yield 13%) and **B** (yield 19%) were assigned on the basis of their UV spectra as the '1-' and '2-' substituted benzotriazoles. No mention is made that there could be three possible isomeric benzotriazole products; in addition to **A** and **B**, there is also structure **C**. The only evidence advanced for the structures of **A** and **B** was derived from UV spectroscopy. This work[24] is limited to a single example and neither substrate scope nor optimization of reaction conditions were investigated.

To the best of our knowledge, the palladium-catalyzed synthesis of pseudohalohydrin esters from *N*-acylbenzotrizoles and epoxides was not previously attempted. We now report an improved protocol for the regiospecific synthesis of β-(benzotriazol-1-yl)ethyl pseudohalohydrin esters **4**, with palladium catalysis under microwave-assisted, solvent-free conditions. Microwave heating is a powerful tool in promoting a variety of applications in organic



Scheme 1 Reported[24] synthesis of a pseudohalohydrin ester from an *N*-acylbenzotrizole and an epoxide

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synthesis and functional-group transformations without solvents. The use of a single-mode cavity microwave synthesizer helps to achieve reproducibility, safety, reduced pollution, and simplicity in processing and handling.[25–31]

We found that palladium-catalyzed thermal reaction of *N*-acylbenzotriazole **1a**[32–34] with epoxide **3a** gave the single regioisomer β-(benzotriazol-1-yl)ethyl ester **4a**. Although, as reported[33] recently, thermal isomerization of **1a** to **1a′**, followed by oxidative addition of **1a′** to palladium(0) gives **1a″**, we found no 1,4-benzoxazine **2a** (Scheme 2).[35]

Our reaction of (1*H*-benzotriazol-1-yl)(4-ethylphenyl)methanone (**1a**) with styrene oxide (**3a**) in the presence of 10 mol% of $Pd(PPh_3)_4$ under microwave irradiation (130 °C, 50 W) for 30 minutes, gave 2-(1*H*-benzotriazol-1-yl)-1-phenylethyl 4-ethylbenzoate (**4a**) as a single regioisomer in 87% yield (Scheme 2). These conditions proved to be generally successful while in the absence of palladium catalyst these reactions did not progress during 30 minutes and prolonged reaction times resulted in decomposition.

Other catalyst systems including anhydrous $CuSO_4$, $CuSO_4·5H_2O$, $Pd(OAc)_2$ were less effective (Table 1, as were lower temperatures, power, and catalyst loadings [100 °C, 20 W and 100 °C, 50 W, 130 °C, 50 W, 5 mol% $Pd(PPh_3)_4$].

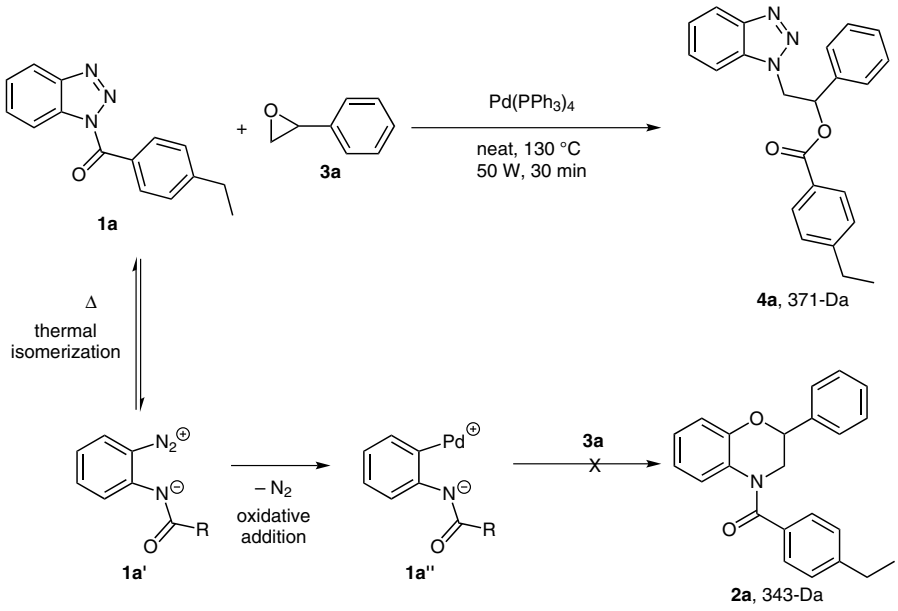
We examined the scope of the palladium-catalyzed reaction of *N*-acylbenzotriazoles **1a**–**f** with epoxides **3a**–**c**, using the optimized conditions as summarized in Table 2. β-(Benzotriazol-1-yl)ethyl esters were obtained as single isomers in 52–87% yields. The reaction proceeded faster with *N*-aroylbenzotriazoles (reaction time, 30 min) than with *N*-alkylbenzotriazoles (reaction time, 60 min) and aromatic as well as alkyl-substituted epoxides were tolerated (Table 2).[36–45]

Table 1 Optimization of Reaction Conditions for **4a**

Entry	Catalyst (mol%)	Reaction conditions	Yield of **4a** (%)
1	none	130 °C, 50 W, 30–90 min	0
2	$Pd(PPh_3)_4$ (10)	130 °C, 50 W, 30 min	87
3	$Pd(Ph_3)_4$ (10)	r.t., $CHCl_3$, 12 h	0
4	$Pd(Ph_3)_4$ (10)	reflux, $CHCl_3$, 12 h	0
5	$Pd(Ph_3)_4$ (10)	130 °C, 12 h	0
6	$Pd(Ph_3)_4$ (5)	130 °C, 50 W, 30 min	45
7	anhyd $CuSO_4$ (10)	130 °C, 50 W, 30 min	0
8	$CuSO_4·5H_2O_4$ (10)	130 °C, 50 W, 30 min	20
9	$Pd(OAc)_2$ (10)	130 °C, 50 W, 90 min	30
10	Ph_3P (10)	130 °C, 50 W, 40 min	35

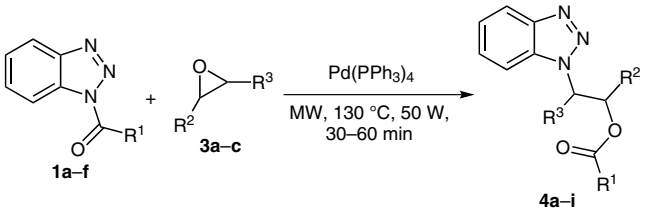
We propose that initially Pd(0) and **1** forms **6**.[46] The interaction of **6** with epoxide **3** forms **6′**, which is then attacked by benzotriazole giving **4** as a single regioisomer (Scheme 3).

The mechanism appears to be similar to the recent report of coupling reaction of acyl halides and epoxides affording halohydrin esters as mixtures of regioisomers (Scheme 4).[1] However, our palladium-catalyzed pathway provided single regioisomers.

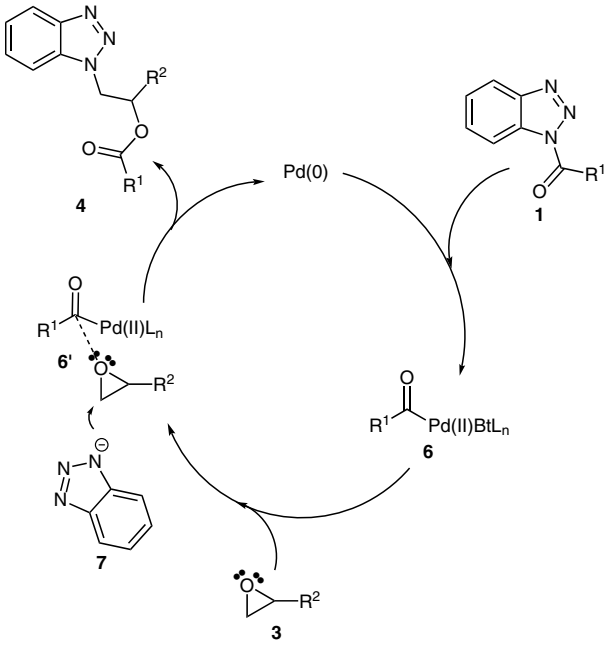


Scheme 2 Palladium-catalyzed thermal reaction of *N*-acylbenzotriazole **1a** with epoxide **3a**

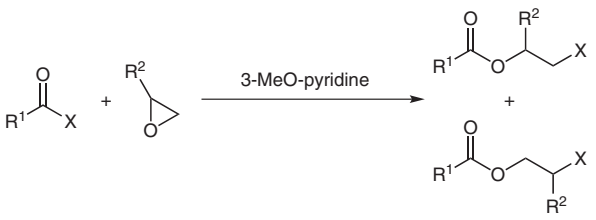
Table 2 Synthesis of β-(Benzotriazol-1-yl)ethyl Esters[36]



Entry	Substrate **1**	Substrate **3**	Yield of **4** (%)
1	**1a** R^1 = 4-EtC_6H_4	**3a** R^2 = Ph, R^3 = H	**4a** 87
2	**1a** R^1 = 4-EtC_6H_4	**3b** R^2 = Ph, R^3 = Ph	**4b** 62
3	**1b** R^1 = $PhCH_2CH_2$	**3c** R^2 = Bu, R^3 = H	**4c** 72
4	**1c** R^1 = 1-naphthyl	**3a** R^2 = Ph, R^3 = H	**4d** 62
5	**1c** R^1 = 1-naphthyl	**3c** R^2 = Bu, R^3 = H	**4e** 73
6	**1d** R^1 = 4-$O_2NC_6H_4$	**3a** R^2 = Ph, R^3 = H	**4f** 70
7	**1e** R^1 = Ph	**3a** R^2 = Ph, R^3 = H	**4g** 75
8	**1e** R^1 = Ph	**3c** R^2 = Bu, R^3 = H	**4h** 76
9	**1f** R^1 = 1-adamantane-CH_2	**3c** R^2 = Bu, R^3 = H	**4i** 52

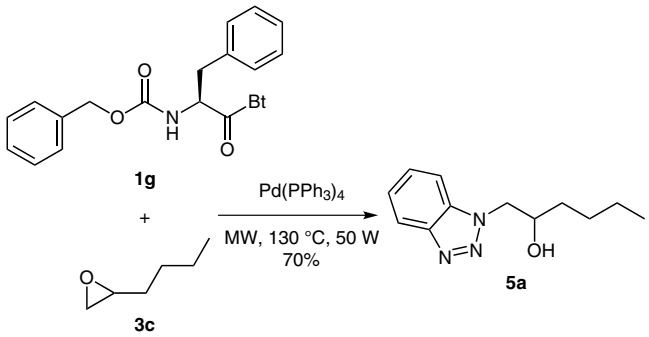


Scheme 3 Possible mechanism



Scheme 4 Acid halides and epoxides in halohydrin ester synthesis[1]

However, reaction of (*Z*)-L-Phe-Bt (**1g**) with **3c** gave **5a**, the alcohol derived from ring opening of the epoxide by the benzotriazole anion (Scheme 5): in **7** the epoxide oxygen becomes protonated.



Scheme 5 Synthesis of pseudohalohydrin **5a**[37,47,48]

In conclusion, Pd-catalyzed reactions of readily available *N*-acylbenzotriazoles with epoxides under solvent-free conditions gives β-(benzotriazol-1-yl)ethyl esters as single regioisomers in an efficient, one-step procedure.

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(36) **General Procedure for the Preparation of β-(Benzotriazol-1-yl)ethyl Esters 4 and Alcohol 5a**
To a mixture of the *N*-acylbenzotriazole **1** (0.20 mmol) and $Pd(PPh_3)_4$ (23.11 mg, 10 mol%) in a microwave tube was added epoxide **3** (1.5 equiv). The mixture was stirred at 130 °C and 50 W for 30 min (*N*-aroylbenzotriazoles) to 60 min (*N*-alkylbenzotriazoles). The residue was dissolved in MeOH and purified by silica gel column chromatography to obtain the corresponding hydrin esters **4**.
(37) **2-(1*H*-Benzotriazol-1-yl)-1-phenylethyl 4-ethylbenzoate (4a)**
Purified by gradient silica gel column chromatography (hexanes to hexanes–EtOAc = 7:3) to obtain a yellow oil, (87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.1 Hz, 1 H), 7.69 (d, *J* = 8.1 Hz, 1 H), 7.27–7.14 (m, 10 H), 7.06–7.01 (m, 1 H), 6.29–6.25 (m, 1 H), 5.00–4.86 (m, 2 H), 2.48 (q, *J* = 7.4 Hz, 2 H), 1.03 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 150.3, 136.7, 133.4, 129.9, 128.9, 128.0, 127.4, 126.3, 125.7, 123.9, 120.0, 109.3, 74.3, 52.8, 29.0, 15.2. HRMS: *m/z* calcd for $C_{23}H_{22}N_3O_2$ $[M + H]^+$: 372.1707; found: 372.1703.
(38) **2-(1*H*-Benzotriazol-1-yl)-1,2-diphenylethyl 4-Ethylbenzoate (4b)**
Purified by gradient silica gel column chromatography (hexanes to hexanes–CH_2Cl_2 = 3:2, then hexanes–CH_2Cl_2 = 1:1) to obtain beige microcrystals (62%); mp 109.0–110.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.68–7.60 (m, 2 H), 7.54–7.47 (m, 1 H), 7.45–7.30 (m, 6 H), 7.27–7.20 (m, 6 H), 7.14–7.11 (m, 2 H), 6.34 (dd, *J* = 9.2, 1.4 Hz, 1 H), 2.82–2.73 (m, 1 H), 2.65 (q, *J* = 7.5 Hz, 2 H), 1.35–1.28 (m, 2 H), 1.22 (td, *J* = 7.8, 2.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 149.9, 136.8, 134.6, 133.3, 130.2, 129.6, 128.8, 128.7, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 127.7, 127.3, 127.2, 126.8, 125.9, 123.9, 120.1, 109.6, 76.8, 67.4, 28.8, 15.1. HRMS: *m/z* calcd for $C_{29}H_{26}N_3O_2$ $[M + H]^+$: 448.2020; found: 448.2022.
(39) **1-{1*H*-Benzo[*d*][1,2,3]triazol-1-yl}hexan-2-yl 3-Phenylpropanoate (4c)**
Purified by gradient silica gel column chromatography (hexanes to hexanes–EtOAc = 4:1) to obtain a yellow oil (72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05–8.01 (m, 1 H), 7.49–7.42 (m, 2 H), 7.36–7.31 (m, 1 H), 7.29–7.07 (m, 5 H), 5.28–5.21 (m, 1 H), 4.74 (dd, *J* = 14.6, 4.8 Hz, 1 H), 4.69 (dd, *J* = 14.5, 6.1 Hz, 1 H), 2.97–2.40 (m, 4 H), 1.59–1.52 (m, 2 H), 1.30–1.19 (m, 4 H), 0.83 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 145.9, 140.27, 133.7, 128.6, 128.4, 127.7, 126.5, 124.2, 120.2, 109.7, 72.5, 50.9, 35.9, 31.5, 30.9, 27.3, 22.6, 14.1.
(40) **2-{1*H*-Benzo[*d*][1,2,3]triazol-1-yl}-1-phenylethyl 1-Naphthoate (4d)**
Purified by gradient silica gel column chromatography (hexanes to hexanes–EtOAc = 9.3:0.7) to obtain a white solid (62%); mp 62.0–63.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60–8.56 (m, 1 H), 8.09–7.97 (m, 3 H), 7.85–7.79 (m, 1 H), 7.50–7.26 (m, 11 H), 6.58 (dd, *J* = 7.5, 4.7 Hz, 1 H), 5.19 (dd, *J* = 14.6, 7.5 Hz, 1 H), 5.11 (dd, *J* = 14.6, 4.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 146.0, 136.9, 134.0, 133.9, 133.6, 131.4, 130.6, 129.2, 128.7, 128.1, 127.7, 126.6, 126.5, 125.7, 124.6, 124.1, 120.3, 109.5, 74.7, 53.1. Anal. Calcd for $C_{25}H_{19}N_3O2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 75.97; H, 5.31; N, 10.45.
(41) **1-{1*H*-Benzo[*d*][1,2,3]triazol-1-yl}hexan-2-yl 1-Naphthoate (4e)**
Purified by gradient silica gel column chromatography (hexanes to EtOAc–hexanes = 9.3:0.7) to obtain a yellow oil (73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64–8.59 (m, 1 H), 8.02–7.89 (m, 3 H), 7.79–7.75 (m, 1 H), 7.51–7.17 (m, 6 H), 5.61–5.53 (m, 1 H), 4.88 (d, *J* = 5.3 Hz, 2 H), 1.78–1.70 (m, 2 H), 1.51–1.22 (m, 4 H), 0.81 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 146.1, 133.9, 133.7, 131.5, 130.5, 128.7, 128.0, 127.6, 126.5, 126.4, 125.7, 124.6, 124.1, 120.2, 109.9, 72.8, 51.0, 31.7, 27.6, 22.6, 14.1. Anal. Calcd for $C_{69}H_{73}N_9O_8$: C, 71.67; H, 6.36; N, 10.90. Found: C, 71.53; H, 6.38; N, 10.93.
(42) **2-{1*H*-Benzo[*d*][1,2,3]triazol-1-yl}-1-phenylethyl 4-Nitrobenzoate (4f)**
Purified by gradient silica gel column chromatography (hexanes to hexanes–EtOAc = 9:1) to obtain a yellow oil (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.11 (m, 7 H), 7.52–7.34 (m, 5 H), 6.44 (dd, *J* = 8.4, 3.6 Hz, 1 H), 4.82 (dd, *J* = 12.0, 8.4 Hz, 1 H), 4.71(dd, *J* =12.2, 3.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 164.0, 151.0, 135.6, 135.2, 135.1, 131.1, 131.0, 129.5, 129.3, 126.9, 123.9, 75.1, 67.3.

(43) **2-(1*H*-Benzotriazol-1-yl)-1-phenylethyl Benzoate (4g)**
Purified by gradient silica gel column chromatography (hexanes to hexanes–EtOAc = 9:1) to obtain a yellow oil (75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.93 (m, 3 H), 7.55–7.27 (m, 11 H), 6.46 (dd, *J* = 7.5, 4.8 Hz, 1 H), 5.15 (dd, *J* = 14.5, 7.3 Hz, 1 H), 5.07 (dd, *J* = 14.5, 4.8, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 145.9, 136.8, 133.6, 129.9, 129.5, 129.2, 129.1, 128.6, 127.6, 126.5, 124.1, 120.2, 109.4, 74.7, 52.9. HRMS: *m/z* calcd for $C_{21}H_{18}N_3O_2$ $[M + H]^+$: 344.1394; found: 344.1384.

(44) **1-{1*H*-Benzo[*d*][1,2,3]triazol-1-yl}hexan-2-yl Benzoate (4h)**
Purified by gradient silica gel column chromatography (hexanes to hexanes–EtOAc = 9:1) to obtain a yellow oil (76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 1 H), 7.91–7.88 (m, 2 H), 7.55–7.49 (m, 2 H), 7.40–7.28 (m, 4 H), 5.55–5.48 (m, 1 H), 4.90 (d, *J* = 5.2 Hz, 2 H), 1.76–1.67 (m, 2 H), 1.47–1.26 (m, 4 H), 0.85 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 146.1, 133.7, 133.5, 129.9, 129.7, 128.6, 127.6, 124.1, 120.2, 109.9, 72.9, 50.9, 31.5, 27.5, 22.6, 14.0. HRMS: *m/z* calcd for $C_{19}H_{22}N_3O_2$ $[M + H]^+$: 324.1707; found: 324.1719.

(45) **1-{1*H*-Benzo[*d*][1,2,3]triazol-1-yl}hexan-2-yl 2-[(3*R*,5*R*,7*R*)-Adamantan-1-yl]acetate (4i)**
Purified by gradient silica gel column chromatography (hexanes to hexanes–EtOAc = 9.3:0.7) to obtain a yellow oil (52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00–7.97 (m, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.47–7.41 (m, 1 H), 7.33–7.28 (m, 1 H), 5.27–5.19 (m, 1 H), 4.72–4.69 (m, 2 H), 2.05–1.88 (m, 3 H), 1.84–1.80 (m, 2 H), 1.63–1.55 (m, 8 H), 1.49–1.46 (m, 2 H), 1.37–1.18 (m, 8 H), 0.82 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 146.0, 133.8, 127.7, 124.1, 120.2, 109.9, 71.9, 50.9, 49.0, 42.5, 42.4, 36.9, 36.8, 32.9, 31.7, 28.8, 28.7, 27.5, 22.6, 14.1. HRMS: *m/z* calcd for $C_{24}H_{33}N_3O_2Na$ $[M + Na]^+$: 418.2465; found: 418.2480.

(46) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley and Sons: New York, **2005**.

(47) **1-(1*H*-Benzotriazol-1-yl)hexan-2-ol (5a)**
Purified by gradient silica gel column chromatography (hexanes to EtOAc–hexanes = 4:1) to obtain a yellow oil[48] (70%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 8.4, 0.9 Hz, 1 H), 7.60 (dd, *J* = 8.7, 0.9 Hz, 1 H), 7.50–7.45 (m, 1 H), 7.36–7.30 (m, 1 H), 4.71–4.64 (m, 2 H), 4.56–4.49 (m, 1 H), 4.25 (br s, 1 H), 1.65–1.34 (m, 6 H), 0.92 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.5, 133.8, 128.5, 127.4, 124.0, 119.7, 109.9, 71.0, 54.0, 34.3, 27.6, 22.6, 14.0. HRMS: *m/z* calcd for $C_{12}H_{17}N_3ONa$ $[M + Na]^+$: 242.1264; found: 242.1266.

(48) Li, Z.; Zhang, Y. *J. Chem. Res., Synop.* **2001**, 522.

