Notes

Palladium-Catalyzed Reaction of *N*-Allylbenzotriazoles with Amines: A Novel Method for the Preparation of Allylamines

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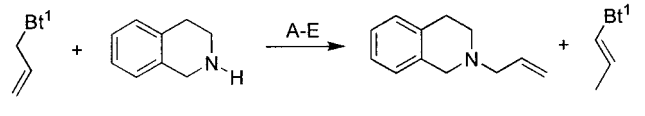
Allylamines are common moieties in biologically active compounds[1] and important intermediates in organic synthesis. Many syntheses of allylamines have been documented including (i) reaction of alkenyl cuprates with iminium salts, α-aminoethers or α-aminothioethers,[2] (ii) reaction of Grignard reagents with allyl-α-aminonitriles,[3] and (iii) the amination of dienes[4] and allylic halides.[1a,5] The most general approach is based on the transition metal catalyzed reaction of amines with allylic substrates including allyl acetates,[6] allyl carboxylates,[7] allyl ethers,[8] allyl alcohols[9]and diethyl allyl phosphates.[10] Besides the aforementioned oxygen-containing leaving groups, amine,[11] nitro,[12] or ammonium[13] moieties have also been employed as the leaving group in transition metal catalyzed allylation.[14] While the amination step in the above reactions usually proceeds efficiently, the convenience of the method depends on the availability of the starting materials.

Scheme 1



1a **2** **3** **4**

1b (Bt^2), Bt^1 = benzotriazol-1-yl, Bt^2 = benzotriazol-2-yl, Bt = Bt^1 + Bt^2

A: $Ni(COD)_2$, dppb, DMF, 80 °C, 4 h, **1a** (100%), **3** (0), **4** (0)
B: $Ni(COD)_2$, dppb, DMF, KOH, 80 °C, 4 h, **3** (60%), **4** (40%)
C: $Pd(PPh_3)_4$, DMF, KOH, 80 °C, 4 h, **1a** (40%), **3** (40%), **4** (20%)
D: $Pd(PPh_3)_4$, MeOH, KOH, reflux, 4 h, **3** (71%), **4** (29%)
E: $Pd(OAc)_2/PPh_3$, MeOH, K_2CO_3 or KOH, refux, 4 h, **3** (100%), **4** (0)
The ratios of **1a**, **3** and **4** were determined by GC

In recent years benzotriazole has been demonstrated to be a useful synthetic auxiliary,[15] with versatility endowed by the benzotriazole group being capable of acting as a nucleofuge,[16] proton activator,[17] electron donor[18] and radical,[19] or carbanion[20] precursor. Since α-mono- and α,α-disubstituted allylbenzotriazoles can be prepared in high yields through lithiation and alkylation of *N*-allylbenzotriazole,[17a] we became interested in exploring the possibility of using benzotriazole as a leaving group in metal-catalyzed allylic amination reaction. The success of such a reaction would be advantageous in terms of both the availability of substrates and the structural diversity of the products.

Results and Discussion

The first step of an allylation is the cleavage of a C−N bond to form the allylic metal complex. However, under the conditions of the recent literature method which used nickel(0) as catalyst in DMF solution at 80 °C,[11c,d] 1-allylbenzotriazole (**1a**) and 1,2,3,4-tetrahydroisoquinoline (**2**), which were chosen as the model substrates, did not react (Scheme 1). When a base was added we were able to detect the desired product **3** by GCMS, but the reaction did not proceed completely. The major side reaction was the isomerization of 1-allylbenzotriazole (**1a**)

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(1) (a) Cheikh, R. B.; Chaabouui, R.; Laurent, A.; Mison, V.; Nafti, A. *Synthesis* **1983**, 685. (b) Kondo, T.; Nakai, H.; Goto, T. *Tetrahedron* **1973**, *29*, 1801.
(2) Germon, C.; Alexakis, A.; Normant, J. F. *Bull. Soc. Chim. Fr., Part 2* **1984**, 377.
(3) Ahlbrecht, H.; Dollinger, H. *Synthesis* **1985**, 743.
(4) Akermark, B.; Akermark, G.; Moberg, C. *J. Organomet. Chem.* **1979**, *164*, 97.
(5) Baruah, J. B.; Samuelson, A. G. *Tetrahedron* **1991**, *47*, 9449.
(6) (a) Walker, W. E.; Manyik, R. M.; Atkins, K. E.; Farmer, M. L. *Tetrahedron Lett.* **1970**, 3817. (b) Shryne, T. M.; Smutny, E. J.; Stevenson, D. P. *Chem. Abstr.* **1970**, *72*, 78373. (c) Murahashi, S.-I.; Tanigawa, Y.; Imada, Y.; Taniguchi, Y. *Tetrahedron Lett.* **1986**, *27*, 227. (d) Flegelova, Z.; Patek, M. *J. Org. Chem.* **1996**, *61*, 6735.
(7) Yamamoto, T.; Ishizu, J.; Yamamoto, A. *J. Am. Chem. Soc.* **1981**, *103*, 6863.
(8) (a) Lardicci, L.; Malanga, C.; Balzano, F.; Menicagli, R. *Tetrahedron* **1994**, *50*, 12953. (b) Bricout, H.; Carpentier, J.-F.; Mortreux, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1863.
(9) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821.
(10) Tanigawa, Y.; Nishimura, K.; Kawasaki A.; Murahashi S.-I. *Tetrahedron Lett.* **1982**, *23*, 5549.
(11) (a) Wenkert, E.; Fernandes, J. B.; Michelotti, E. L.; Swindell, C. S. *Synthesis* **1983**, 701. (b) Murahashi, S.-I.; Imada, Y.; Nishimura, K. *Tetrahedron* **1994**, *50*, 453. (c) Trost, B. M.; Spagnol, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083. (d) Bricout H.; Carpentier, J.-F.; Mortreux, A. *J. Chem. Soc., Chem. Commun.* **1997**, 1393.
(12) (a) Tamura, R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 3727. (b) Ono, N.; Hamamoto, I.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1982**, 821. (c) Tamura, R.; Hayashi, K.; Kai, Y.; Oda, D. *Tetrahedron Lett.* **1984**, *25*, 4437.
(13) (a) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1980**, *45*, 2741. (b) Hosomi, A.; Hoashi, K.; Kohra, S.; Tominaga, Y.; Otaka, K.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1987**, 570. (c) Moreno-Manas, M.; Morral, L.; Pleixats, R. *J. Heterocycl. Chem.* **1997**, *34*, 241.
(14) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 585.
(15) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. *Chem. Rev.* **1998**, *98*, 409.
(16) (a) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683. (b) Katritzky, A. R.; Fan, W.-Q. *J. Org. Chem.* **1990**, *55*, 3205.
(17) (a) Katritzky, A. R.; Li, J.; Malhotra, N. *Liebigs Ann. Chem.* **1992**, 843. (b) Katritzky, A. R.; Wu, J.; Kuzmierkiewicz, W.; Rachwal, S. *Liebigs Ann. Chem.* **1994**, 1. (c) Katritzky, A. R.; Wu, H.; Xie, L.; Jiang, J. *J. Heterocycl. Chem.* **1995**, *32*, 595.
(18) (a) Katritzky, A. R.; Rachwal, S.; Caster, K. C.; Mahni, F.; Law, K. W.; Rubio, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 781. (b) Katritzky, A. R.; Lan, X.; Fan, W.-Q. *Synthesis* **1994**, 445.
(19) (a) Aurrecoechea, J. M.; Lopez, B.; Fernandez, A.; Arrieta, A.; Cossio, F. P. *J. Org. Chem.* **1997**, *62*, 1125. (b) Aurrecoechea, J. M.; Fernandez-Acebes, A. *Tetrahedron Lett.* **1993**, *34*, 549.
(20) (a) Katritzky, A. R.; Qi, M.*J. Org. Chem.* **1997**, *62*, 4116. (b) Katritzky, A. R.; Qi, M.; Feng, D.; Nichols, D. A. *J. Org. Chem.* **1997**, *62*, 4121.

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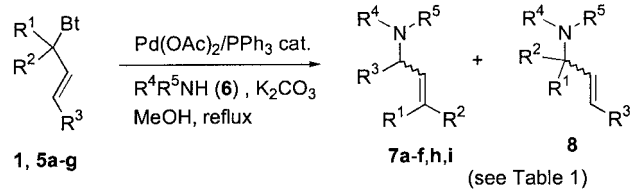
Scheme 2



5	a	b	c	d	e	f	g
R^1	Me	Et	*n*-Bu	Bn	*n*-Bu	H	H
R^2	H	H	H	H	*n*-Bu	H	H
R^3	H	H	H	H	H	Me	Ph

Table 1. Preparation of Allylamines 7 and 8

start matl	product	R^1	R^2	R^3	R^4	R^5	yield (%)
5a	**7a**	Me	H	H	*o*-$CH_2C_6H_4(CH_2)_2$−		85
5b	**7b**	Et	H	H	*n*-C_8H_{17}	Me	80
5c	**7c**	*n*-Bu	H	H	Bn	Bn	70
5d	**7d**	Bn	H	H	Et	Et	70
5e	**7e**	*n*-Bu	*n*-Bu	H	−$(CH_2)_5$−		75
5f	**7f**	H	H	Me	*o*-$CH_2C_6H_4(CH_2)_2$−		20[a]
5g	**8**	H	H	Ph	−$(CH_2)_5$−		75
1	**7h**	H	H	H	Bn	Bn	80
1	**7i**	H	H	H	*n*-C_8H_{17}	*n*-C_8H_{17}	87

[a] 70% of **7a** also found.

to 1-(propenyl)benzotriazole (**4**). We tested other catalysts [$Pd(PPh_3)_4$, $Pd(OAc)_2/PPh_3$] and solvents (THF, toluene, CH_3CN, 1,4-dioxane, MeOH, EtOH, *n*-BuOH, and DMA) and found that best conditions for the allyl amination were using methanol as solvent, K_2CO_3 or KOH as base, and $Pd(OAc)_2$ (3 mol %) and PPh_3 (9 mol %) as catalyst. Without $Pd(OAc)_2/PPh_3$ catalyst, the reaction of **1a** and **2** only gave isomerization product **4**.

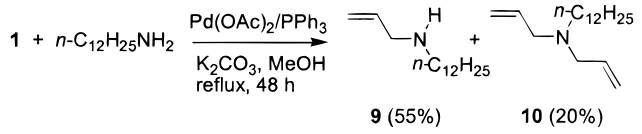
Under such conditions the isomeric 2-allylbenzotriazole (**1b**) also reacts with amines and therefore it is not necessary to separate **1a** and **1b**. The mixture **1a** and **1b** reacts with secondary amines such as dibenzylamine and dioctylamine to give tertiary allylamines **7h**,**i** in good yields (Scheme 2, Table 1); however, *N*,*N*-diphenylamine failed to react with **1** to produce the corresponding allylamine.

Under the standard reaction conditions, α-mono- and α,α-disubstituted allylbenzotriazoles **5a**−**e** reacted with various secondary amines to give the allylamines **7a**−**e** in good yields (Scheme 2, Table 1). The reaction proceeds regiospecifically, with amine attack at the least substituted carbon to give only the γ-amination product. The starting materials **5a**−**e** were prepared from *N*-allylbenzotriazole (**1**) and alkyl bromides in almost quantitatively yields;[17a] the crude products were used for the subsequent reactions without further purification.

γ-Substituted allylbenzotriazoles **5f**,**g** can also be employed in this reaction. 1-(Benzotriazol-1-yl)-2-butene (**5f**) reacted with **2** to give a mixture of α- and γ-amination products **7a** and **7f**, while the reaction of **5g** and piperidine afforded the α-amination product **8** selectively. The reaction probably proceeds through the allylic-palladium complex intermediate, and the amine attacks the least substituted terminus of the allyl group.[14]

Compounds **7a**−**d** were isolated as mixtures of *E*- and *Z*-isomers; the ratio of the two isomers was determined by GC analysis (from 80/20 to 98/2). The definite assignment of these isomers are difficult, as the alkene protons in all of these compounds overlapped in their ^1H NMR spectra. For compound **8**, only one isomer was obtained and the coupling constant of the alkene proton is 15.9 Hz, so we concluded that **8** is the *E*-alkene and by analogy deduced that the major isomers in **7a**−**d** are also the *E*-alkenes.

Scheme 3



When a primary amine was used as the nucleophile, both mono- (**9**) and diallylamines (**10**) were formed (Scheme 3). However, under the standard conditions, the reaction of **5g** and ammonia failed to produce the desired primary allylamine.

In conclusion, we found that benzotriazole can be used as a leaving group in the palladium-catalyzed allyl amination. This new methodology provides a general access to a wide range of allylamines. Compared to the previous available methods, a practical advantage of the present route is that *N*-(substituted allyl)benzotriazoles can be readily prepared.

Experimental Section

General. Compounds **5a**−**g** were prepared by the literature methods.[17a] For NMR and other chemical information see our previous paper.[20a]

General Procedure for the Preparation of Allylamines 3, 7a−**f**,**h**,**i, and 8**−**10**. Under argon, a mixture of allylbenzotriazole (5.3 mmol), amine (1.1 g, 5.8 mmol), $Pd(OAc)_2$ (40 mg, 0.18 mmol), PPh_3 (140 mg, 0.53 mmol), and K_2CO_3 (1.0 g) in MeOH (15 mL) was refluxed for 4−48 h. The reaction mixture was cooled to room temperature, quenched with water (20 mL), and extracted with ether (3 × 40 mL). The solvent was removed under vacuum, and the residual oil was purified by column chromatography on neutral alumina (hexane:triethylamine 100:3) to afford the desired products.

***N*-Allyl-1,2,3,4-tetrahydroisoquinoline (3)**:[21] 85% yield, colorless oil; ^1H NMR δ 2.75 (t, 2H, J = 5.9 Hz), 2.93 (t, 2H, J = 5.7 Hz), 3.18 (d, 2H, J = 6.4 Hz), 3.64 (s, 2H), 5.22 (d, 1H, J = 10.4 Hz), 5.26 (d, 1H, J = 18.3 Hz), 5.93−6.02 (m, 1H), 7.02−7.13 (m, 4H); ^{13}C NMR d 29.0, 50.2, 55.9, 61.4, 117.7, 125.5, 126.0, 126.5, 128.6, 134.2, 134.7, 135.3.

***N*-(2-Butenyl)-1,2,3,4-terahydroisoquinoline (7a)**: colorless oil; a mixture of *E*- and *Z*-isomers (*E*/*Z* = 80/20); ^1H NMR δ 1.73 (d, 3H, J = 5.4 Hz), 2.73 (t, 2H, J = 5.9 Hz), 2,89 (t, 2H, J = 5.3 Hz), 3.10 (d, 2H, J = 5.4 Hz) [3.17 (d, 2H, J = 5.4 Hz, *E*-isomer)], 3.60 (s, 2H) [3.61 (s, 2H, *Z*-isomer)], 5.62−5.67 (m, 2H), 7.01−7.33 (m, 4H); ^{13}C NMR δ 17.8, 29.1 [29.11, *Z*-isomer], 50.5, 55.9 [55.4, *Z*-isomer], 60.6, 125.4, 126.0, 126.5, 127.8, 128.6, 128.9, 134.3, 134.6. Anal. Calcd for $C_{19}H_{39}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.19; H, 9.37; N, 7.48.

***N*-Methyl-*N*-(2-pentenyl)octylamine (7b)**: colorless oil; a mixture of *E*- and *Z*-isomers (*E*/*Z* = 90/10); ^1H NMR δ 0.91−1.03 (m, 6H), 1.31−1.49 (m, 12H), 2.06−2.08 (m, 2H), 2.22 (s, 3H), 2.31−2.33 (m, 2H), 2.94−2.96 (m, 2H) [3.01−3.03 (m, 2H, *Z*-isomer)], 5.51−5.62 (m, 2H); ^{13}C NMR δ 13.6, 14.1, 22.7, 25.4, 27.4, 27.5, 29.3, 29.6, 31.8, 42.0, 57.4 [54.2, *Z*-isomer], 60.1, 126.1, 135.5 [134.3, *Z*-isomer]; HRMS (EI) calcd for $C_{14}H_{29}N$ 211.2300, found 211.2414.

***N*,*N*-Dibenzyl-2-heptenylamine (7c)**: colorless oil; a mixture of *E*- and *Z*-isomers (*E*/*Z* = 80/20); ^1H NMR δ 0.91 (t, 3H, J = 4.6 Hz), 1.32−1.37 (m, 4H), 2.02−2.06 (m, 2H), 3.01 (d, 2H,

(21) Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209.

J = 6.3 Hz) [3.87 (d, 2H, J = 5.9 Hz, *Z*-isomer)], 3.57 (s, 4H) [3.33 (s, 4H, *Z*-isomer)], 5.53−5.59 (m, 2H), 7.21−7.39 (m, 10H); ^{13}C NMR δ 13.9, 22.2, 31.6, 32.1, 55.5, 57.6, 126.7, 127.1, 128.1, 128.8, 134.1, 139.9. Anal. Calcd for $C_{21}H_{27}N$: C, 85.95; H, 9.27; N, 4.77. Found: C, 86.36; H, 9.81; N, 5.03.

***N*,*N*-Diethyl-4-phenyl-2-butenylamine** (**7d**): colorless oil; a mixture of *Z*- and *E*-isomers (*E*/*Z* = 98/2); ^{1}H NMR δ 1.03 (t, 6H, J = 7.1 Hz), 2.52 (q, 4H, J = 7.2 Hz), 3.07 (d, 2H, J = 6.5 Hz), 3.37 (d, 2H, J = 6.5 Hz), 5.59−5.69 (m, 2H), 7.16−7.32 (m, 5H); ^{13}C NMR δ 11.6, 38.9, 46.5, 55.0, 125.9, 128.3, 128.4, 128.7, 132.0, 141.3. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.65; H, 10.19; N, 6.64.

1-(1-Piperidinyl)-3-butyl-2-heptene (**7e**): colorless oil; ^{1}H NMR δ 0.89−0.93 (m, 6H), 1.31−1.61 (m, 14H), 1.99 (t, 4H, J = 7.0 Hz), 2.26−2.46 (m, 4H), 2.93 (d, 2H, J = 6.6 Hz), 5.24 (t, 1H, J = 5.7 Hz); ^{13}C NMR δ 13.9, 14.0, 22.5, 22.8, 24.5, 26.0, 30.2, 30.3, 30.7, 36.6, 54.6, 56.7, 121.4, 142.4. Anal. Calcd for $C_{16}H_{31}N$: C, 80.94; H, 13.16; N, 5.90. Found: C, 81.07; H, 13.51; N, 6.18.

***N*-(1-Buten-3-yl)-1,2,3,4-terahydro-isoquinoline** (**7f**): colorless oil; ^{1}H NMR δ 1.28 (d, 3H, J = 6.6 Hz), 2.73−2.75 (m, 2H), 2.86−2.89 (m, 2H), 2.92−3.12 (m, 1H), 3.74 (s, 2H), 5.16 (d, 1H, J = 9.5 Hz), 5.21 (d, 1H, J = 19.7 Hz), 5.91−5.98 (m, 1H), 7.03−7.12 (m, 4H); ^{13}C NMR δ 17.2, 29.6, 47.5, 52.7, 62.4, 115.6, 125.4, 125.9, 126.0, 126.6, 126.7, 128.6, 140.4. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.17; H, 9.37; N, 7.48.

***N*,*N*-Dibenzyllallylamine** (**7h**): colorless oil; ^{1}H NMR δ 3.10 (d, 2H, J = 5.4 Hz), 3.61 (s, 4H), 5.15 (d, 1H, J = 10.2 Hz), 5.25 (d, 1H, J = 18.7 Hz), 5.88−6.02 (m, 1H), 7.25−7.45 (m, 10H);^{13}C NMR δ 56.3, 57.7, 117.3, 126.8, 128.2, 128.68, 128.73, 136.0. Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 85.56; H, 7.92; N, 5.28.

***N*,*N*-Dioctylallylamine** (**7i**): colorless oil; ^{1}H NMR δ 0.88 (t, 6H, J = 6.6 Hz), 1.18−1.43 (m, 24H), 2.39 (t, 4H, J = 7.7 Hz), 3.07 (d, 2H, J = 6.4 Hz), 5.09 (d, 1H, J = 10.7 Hz), 5.15 (d, 1H, J = 18.4 Hz), 5.85−5.88 (m, 1H); ^{13}C NMR δ 14.1, 22.7, 27.0, 27.6, 29.3, 29.6, 31.9, 53.8, 57.3, 116.7, 136.3. Anal. Calcd for $C_{19}H_{39}N$: C, 81.06; H, 13.96; N, 4.98. Found: C, 81.33; H, 13.77; N, 5.20.

***N*-(3-Phenylallyl)-piperidine** (**8**): colorless oil; ^{1}H NMR δ 1.45−1.59 (m, 2H), 1.61−1.65 (m, 4H), 2.35−2.55 (m, 4H), 3.14 (d, 2H, J = 6.6 Hz), 6.34−6.35 (m, 1H), 6.50 (d, 1H, J = 15.9 Hz), 7.2−7.4 (m, 5H); ^{13}C NMR δ 24.2, 25.8, 54.4, 61.7, 126.2, 127.0, 127.2, 128.4, 132.6, 137.0. Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.21; H, 9.60; N, 6.99.

***N*-Allyldodecylamine** (**9**): 55% yield, colorless oil; ^{1}H NMR δ 0.90 (t, 3H, J = 6.0 Hz), 1.22−1.40 (m, 18H), 1.45−1.55 (m, 2H), 2.61 (t, 2H, J = 7.1 Hz), 3.26 (d, 2H, J = 6.1 Hz), 5.09 (d, 1H, J = 10.2 Hz), 5.17 (d, 1H, J = 17.1 Hz), 5.89−5.95 (m, 1H); ^{13}C NMR δ 14.1, 22.7, 27.4, 29.3, 29.6, 30.2, 31.9, 49.5, 52.6, 115.5, 137.1. Anal. Calcd for $C_{15}H_{31}N$: C, 79.92; H, 13.86; N, 6.21. Found: C, 80.25; H, 13.56; N, 5.91.

***N*,*N*-Diallyldodecylamine** (**10**): 20% yield, colorless oil; ^{1}H NMR δ 0.88 (t, 3H, J = 5.4 Hz), 1.22−1.32 (m, 18H), 1.40−1.44 (m, 2H), 2.40 (t, 2H, J = 6.6 Hz), 3.07 (d, 4H, J = 6.3 Hz), 5.10 (d, 2H, J = 9.2 Hz), 5.14 (d, 2H, J = 16.4 Hz), 5.81−5.87 (m, 2H); ^{13}C NMR δ 14.1, 22.7, 26.9, 27.5, 29.3, 29.55, 29.6, 31.9, 53.4, 56.9, 117.1, 135.9. Anal. Calcd for $C_{18}H_{35}N$: C, 81.44; H, 13.29; N, 5.28. Found: C, 81.46; H, 13.55; N, 5.33.

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