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Click-Dimerized *Cinchona* Alkaloids

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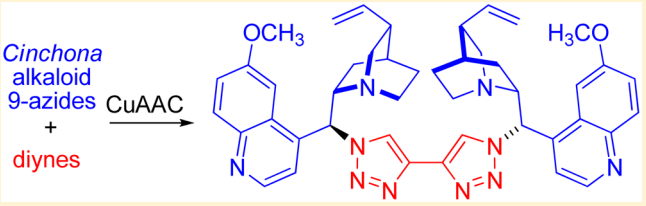
Supporting Information

ABSTRACT: A series of *Cinchona* alkaloid-derived dimers were obtained in high yields in copper-catalyzed 1,3-dipolar "click" cycloaddition using bis(TMS)butadiyne and other bivalent alkynes. The products with bitriazole linkers were effective ligands for asymmetric copper-catalyzed Michael addition. It was shown that the presence of such linker was responsible for effective chirality transfer.



Synthetic dimeric *Cinchona* alkaloids,[1] and in particular the Sharpless dihydroxylation ligands[2−4] have found wide use in enantioselective synthesis. Their versatile applications include both metal-catalyzed reactions and organocatalysis.[1−5] In these dimers the alkaloid residues are connected via an ether bond with a heterocyclic linker. The length of the linker (5−6 atoms between C9 centers) determines the size of the cavity and translates to enantioselective performance.

Another concept significantly developed by Sharpless—*click-chemistry*—using copper-catalyzed azide alkyne cycloaddition (CuAAC)[6−8] has been proven as an efficient way of conjugating molecules relevant to many areas of biomedical research.[9] Most often, however, the lone triazole linker unit has little further use. In contrast, a combination of triazole with another heterocycle gives systems of rich coordination chemistry.[10] The use of bifunctional components of CuAAC to make dimeric compounds has been exploited to some extent.[11,12] Also, molecules with more than one triazole unit have been used as *N*,*N*-donating ligands,[13] dicarbene ligands,[14] and as anion binders.[15] Here we report an application of *click-chemistry* to obtain a new class of *C*2-symmetric dimeric *Cinchona* alkaloids with triazole-based linkers.

The *Cinchona* alkaloid 9-azides **1** were conveniently prepared using a known two-step procedure involving S_N2 substitution of respective alkaloid 9-methanesulfonate with sodium azide.[16] Consequently, azides of *epi* configuration (i.e., 8*S*,9*S* or 8*R*,9*R*), ***e*QN-1**, ***e*CD-1**, and ***e*DHQD-1**, were obtained starting from quinine, cinchonidine, and 10,11-dihydroquinidine, while azides of native configuration (i.e., 8*S*,9*R* or 8*R*,9*S*), **QN-1**, **DHQD-1**, and **DHCN-1**, were obtained from *epi*-quinine, *epi*-10,11-dihydroquinidine, and *epi*-10,11-dihydrocinchonine, respectively. Alternatively, the azides could be obtained in just one step via the Mitsunobu reaction.[17] On the other hand, the bivalent terminal alkynes or their TMS-protected derivatives were commercially available or could be obtained from the respective aryl halides and TMS-acetylene in the Sonogashira reactions.[18−20] For convenience, the TMS groups were not removed from the terminal alkynes prior to the coupling reaction, instead a one pot procedure was applied (Scheme 1). Moreover, such approach alleviated the need to handle instable 1,3-butadiyne.[21] Since the double cycloaddition products were expected to form coordination compounds with copper, the reaction was terminated by the addition of aqueous sodium sulfide, which helped remove most of the metal from the reaction mixture during workup.

The reactions of *epi*-azido quinine (***e*QN-1**) with dialkynes proceeded and the expected very good yields were obtained (Scheme 1). The less congested products were obtained nearly quantitatively, whereas the much more sterically demanding transformations of 1,2-diethynyl-benzene and 1,8-diethynyl-naphthalene derivatives were still very efficient (91−96% per cyclization step). In most cases chromatography was needed to remove the excess of one of the applied reagents. Only the isolation of ***e*QN-6** required careful separation from additional byproducts. More bitriazole dimer **2** analogues were obtained from other *Cinchona* alkaloid 9-azides (Table 1). However, in case of azides of 8*R*,9*S* configuration (**DHQD-1** and **DHCN-1**), derived from dihydroquinidine and dihydrocinchonine,[22] the dimeric products **2** were obtained in rather low yields (47 and 22%, respectively). This observation is correlated with poorer accessibility of the 9-substituent in the quinidine derivatives due to steric interactions also observed for other transformations of the alkaloids.

In order to obtain monomeric analogue of ***e*QN-2**, the alkaloid 9-azide was reacted with an excess of TMS-acetylene under CuAAC conditions. The reaction proceeded with excellent yield and the products were obtained in high purity directly after workup. The TMS group was removed with dilute HF in water/MeOH.

The shortest link between the alkaloid units was constructed from 1,3-butadiyne derivative. The overall length (6 atoms in between the C-9 centers) is the same as in the Sharpless-type aryl ethers (Figure 1). The bitriazole linker is expected to adopt a planar conformation to ensure best orbital overlapping between the two 1,2,3-triazole units. Although there are two conformations of this system, the *anti* conformation is significantly lower in energy (ca. 6 kcal/mol by DFT

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Scheme 1. Synthesis of Quinine *Click* Dimers

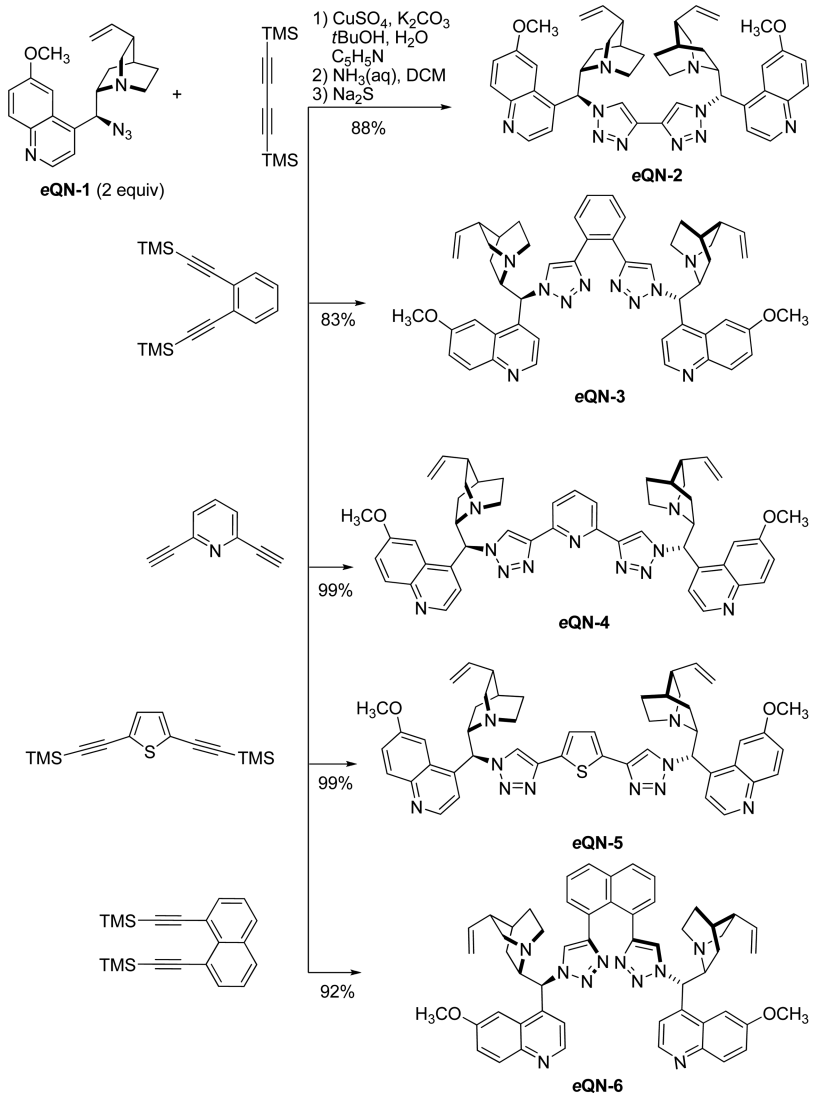
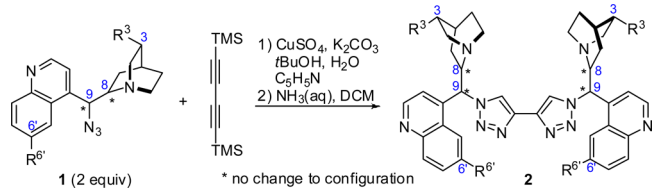


Table 1. Synthesis of Bitriazole Dimers 2



alkaloid azide core, **1**	$R^{6'}$	R^3	configuration	product	yield
epi-quinine	OCH_3	C_2H_3	8*S*,9*S*	***e*QN-2**	88
nat-quininie	OCH_3	C_2H_3	8*S*,9*R*	**QN-2**	74
epi-dihydroquinidine	OCH_3	Et	8*R*,9*R*	***e*DHQD-2**	78
nat-dihydroquinidine	OCH_3	Et	8*R*,9*S*	**DHQD-2**	47
epi-cinchonidine	H	C_2H_3	8*S*,9*S*	***e*CD-2**	67
nat-dihydrocinchonine	H	Et	8*R*,9*S*	**DHCN-2**	22

calculation). However, the *syn* conformation is expected to be prevalent when complexed with metal ions or protonated. The DFT calculations at the B3LYP/CC-pVDZ level of theory for the gas phase suggest that *C*2-symmetric conformation is overall lowest in energy (Figure 2). The N−C9−C8−N and N−C9−C4′−C3′diahedral angles were +44.3° and −18.8°, respectively. In this *anti-open* conformation the two quinuclidine nitrogen face each other at a distance of about 8 Å, while another cavity between the two nearly parallel quinoline rings measures ca. 8.5 Å. The well resolved NMR spectra for ***e*QN-2** as well as good correlation of experimental ^1H and ^{13}C chemical shifts and DFT calculated isotropic shieldings (see SI)

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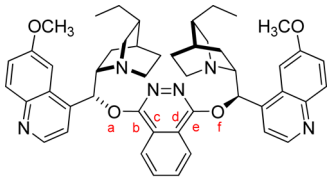
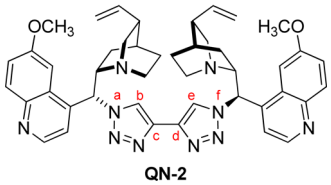


DHQ$_2$PHAL



QN-2

Figure 1. Comparison of Sharpless ligand and **QN-2**.

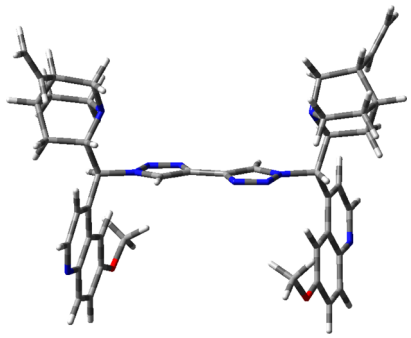


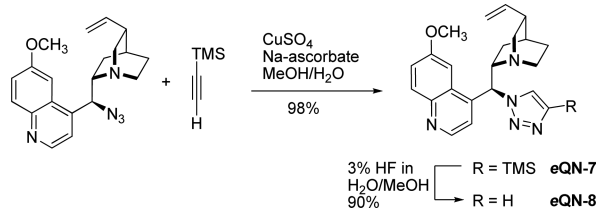
Figure 2. Lowest energy conformer of ***e*QN-2** optimized at the DFT/B3LYP/CC-pVDZ level of theory.

suggest that the conformation is prevalent in solution. In contrast, dimers with extended linkers, ***e*QN-3**, ***e*QN-4**, and particularly ***e*QN-6**, display broadened spectra. In the case of 1,8-bis(triazolyl)naphthalene system in ***e*QN-6**, the planar orientation is no longer possible and high congestion constricts rotation along a few single bonds resulting in complex conformation equilibria and ^{1}H NMR spectral changes observed between 45 and −45 °C (Figure S12, SI).

The obtained dimers **2** are analogous to the Sharpless ligands (Figure 1) of a proven very broad application scope in catalysis.[1,4] On the other hand, new metal chelating sites within bitriazole (**2**) and ditriazolyl-aryl (**3** to **6**) units are reminiscent of *C*2-symmetric BOX-ligands.[23] Both these structural similarities within the obtained ligands are of relevance to asymmetric catalysis. However, there is little data[13] on such application of bitriazole systems. The attempted osmium-catalyzed dihydroxylation of stilbene and aminohydroxylation of ethyl cinammate in the presence of ***e*QN-2** led to marginal or no product formation. However, the bitriazole is known to coordinate copper(II),[10] and the formed complex could further bind dicarbonyl compounds. Thus, the alkaloid dimers were investigated in the copper-mediated asymmetric Michael addition. For catalytic assay, ethyl (*E*)-2-oxo-4-phenyl-3-butenoate (**9**) was chosen as a Michael acceptor.[24] Its reaction with 1,3-dicarbonyl compounds results in two sequential additions giving a cyclic hemiacetal **10**[25−30] (Scheme 2). This heterocyclic product shares framework with many natural compounds[31−33] and is an attractive intermediate.[34]

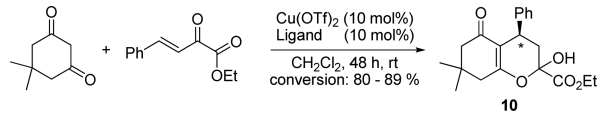
The Michael reaction of **9** and dimedone, catalyzed by 10 mol% of complex formed *in situ* from bitriazole dimer ***e*QN-2**

Scheme 2. Synthesis of Triazolyl-quinine *e*QN-8



and copper(II) triflate run in dichloromethane, yielded 62% of product **10** in an enantioselective manner (e.r. 87:13; Table 2).

Table 2. Application of Dimeric *Cinchona* Alkaloids in Copper-Catalyzed Asymmetric Michael Addition



10

entry	ligand (10 mol %)	e.r. (*R*:*S*)
1	***e*QN-2**	87:13
2	***e*QN-3**	52:48
3	***e*QN-4**	51:49
4	***e*QN-5**	52:48
5	***e*QN-6**	49:51
6	***e*QN-8**	57:43
7	(QN)$_2$PHAL	50:50
8	quinine	51:49
9[a]	***e*QN-2**	53:47
10[b]	***e*QN-2**	63:37
11	**QN-2**	59:41
12	***e*CD-2**	82:18
13	***e*DHQD-2**	21:79
14	**DHQD-2**	49:51

[a]Without copper salt. [b]Ligand to metal ratio 2:1.

The process was very sensitive to the transition metal salt used, and the best results were obtained with copper triflate (for the details, see SI). Triazole ligands with spacers, ***e*QN-3** through ***e*QN-6**, failed to transfer chirality to the product **10** (Table 2, entries 2−6). Also the application of analogous monomeric triazole derivative ***e*QN-8** led to racemate. Similarly, the complexes of Sharpless asymmetric dihydroxylation ligands with phthalazine ((QN)$_2$PHAL) and anthraquinone cores were ineffective, providing nearly racemic product (ee up to 11%). Thus, the reaction clearly requires the bitriazole system. The tested reaction can also be catalyzed with a base. Consequently, the presence of basic sites[25] in bare ligand ***e*QN-2** results in organocatalyzed process in the absence of copper, however the reaction proceeds without stereoselection (Table 2, entry 9). Also the use of higher ligand to metal ratio (i.e., 2:1) resulted in a significantly deteriorated selectivity.

The relative configuration at C8 and C9 stereogenic centers in the *Cinchona* dimers **2** determines the structure by differently arranging basic quinuclidine sites and sterically shielding quinoline rings around the bitriazole-bound metal center, thus translated to a pronounced effect on enantioselectivity. Dimers of 9-*epi* configuration (8*S*,9*S* and 8*R*,9*R*) provided high enantiomeric excess, whereas ligands with 9-native configuration (8*S*,9*R* and 8*R*,9*S*) gave at most 18 %ee (Table 2, entries 1 and 13 vs entries 11 and 14). On the other hand, the choice of pseudoenantiomeric catalysts, ***e*QN-2** (8*S*,9*S*) and

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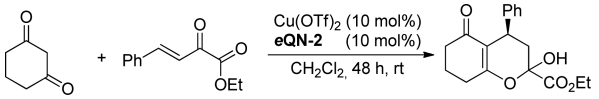
*e*DHQD-2 (8*R*,9*R*), allowed for both antipodes of **10** to be obtained in similar enantioselectivity. The use of quinine and cinchonidine-derived dimers, ***e*QN-2** and ***e*CD-2**, led to very similar enantioselectivity (e.r. 87:13 vs 82:18, respectively), thus indicating minor influence of the 6′-methoxy groups.

In the Michael reaction catalyzed by ***e*QN-2**/$Cu(OTf)_2$, the change of the nucleophile from dimedone to 1,3-cyclohexanedione provided the corresponding product (*R*)-**11** with slightly improved enantioselectivity (Scheme 3). However, the application of other (*E*)-2-oxo-3-butenoic acid alkyl esters led to diminished stereocontrol.

Scheme 3. Michael Addition of 1,3-Cyclohexanedione Catalyzed by an *in situ* Formed *e*QN-2/$Cu(OTf)_2$ Complex



11, 73%, e.r. = 91 :9

All these results prove the applicability of an easily obtainable chiral bitriazole system for copper-catalyzed transformations. The failure of structurally similar phthalazine dimers suggests that the bitriazole is a likely coordinating site, rather than just a spacer which forms a distant environment for other catalytically active sites. Without significant loss of selectivity, the system could neither be simplified to a single triazole unit nor expanded with additional rings separating the system.

EXPERIMENTAL SECTION

General Procedure for Bitriazole Dimers 2. The appropriate 9-azido-9-deoxy-alkaloid[16] (1.25 mmol, 1 equiv) and 1,4-bis-(trimethylsilyl)-1,3-butadiyne (125 mg, 0.64 mmol, 0.51 equiv) were suspended in a mixture of *tert*-butanol (2 mL) and water (1 mL). Pyridine (0.2 mL) was added followed by $CuSO_4 \cdot 5H_2O$ (51 mg, 0.2 mmol, 0.16 equiv), sodium ascorbate (0.13 g, 0.65 mmol, 0.52 equiv), and potassium carbonate (0.14 g, 1.0 mmol, 0.8 equiv). After addition the mixture turned yellow, then brown, and finally formed a red gel. After 18 h of stirring, the mixture was diluted with dichloromethane (5 mL) and aqueous ammonia (25% soln., 0.5 mL) and stirred for an additional 12 h. Then, a solution of sodium sulfide (satd. aqueous, 0.2 mL) was added, and after 5 min the mixture passed through a pad of silica gel and washed with chlorofom/methanol (10:1 v/v, 50 mL), and evaporated giving crude material rich in **2**. The products were purified on silica gel (chlorofom/methanol 15:1 or 20:1 v/v) to give white or off-white crystalline solids. On heating at above 160 °C, the products **2** undergo visible transition to semisolids and then melt with decomposition in broad temperature ranges. Recrystallization (MeOH) did not affect this behavior.

1,1′-Di((8*S*,9*S*)-6′-methoxycinchonan-9-yl)-4,4′-bi-1,2,3-triazole (*e*QN-2). Following the general procedure, starting from 9-*epi*-9-azido-9-deoxy-quinine[16] (***e*QN-1**, 0.436 g, 1.25 mmol), the crude product of approximately 95% purity (NMR), was purified on silica gel ($CHCl_3$/MeOH 15:1 v/v) to give 409 mg (88%) as white crystalline solid. $[\alpha]_D^{25} = -205$ (*c* 0.98, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.5 Hz, 2H), 7.96 (d, *J* = 9.2 Hz, 2H), 7.94 (br. s, 2H), 7.49 (s, 2H), 7.44 (d, *J* = 4.5 Hz, 2H), 7.29 (d, *J* = 9.2 Hz, 2H), 6.42 (d, *J* = 11.1 Hz, 2H), 5.83−5.89 (m, 2H), 5.03 (d, *J* = 11.4 Hz, 2H), 5.03 (d, *J* = 16.2 Hz, 2H), 3.84 (s, 6H), 3.80−3.85 (m, 2H), 3.35−3.41 (m, 2H), 3.09 (dd, *J* = 13.6, 10.5 Hz, 2H), 2.58−2.68 (m, 4H), 2.25 (br. s, 2H), 1.86−1.92 (m, 2H), 1.70 (br. s, 2H), 1.49−1.56 (m, 4H), 0.84−0.88 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 147.3, 145.0, 141.4, 140.0, 138.8, 132.0, 128.2, 122.4, 119.23, 119.16, 114.7, 100.8, 60.8, 57.9, 56.1, 55.8, 41.0, 39.2, 27.73, 27.72, 27.64. HR-MS (ESI-TOF) *m*/*z* calculated for $[C_{44}H_{48}N_{10}O_2+H]^+$: 749.4034; found: 749.4032

1,1′-Di((8*S*,9*R*)-6′-methoxycinchonan-9-yl)-4,4′-bi-1,2,3-triazole (QN-2). Following the general procedure, starting from 9*R*-azido-9-deoxyquinine (**QN-1**, 436 mg, 1.25 mmol), 346 mg of product (74%) was obtained after chromatography ($CHCl_3$/MeOH 20:1 v/v) as off-white solid. $[\alpha]_D^{25} = +217$ (*c* 1.06, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (d, *J* = 4.6 Hz, 2H), 7.94 (d, *J* = 9.1 Hz, 2H), 7.75 (s, 2H), 7.65 (d, *J* = 4.6 Hz, 2H), 7.33 (d, *J* = 2.1 Hz, 2H), 7.25 (dd, *J* = 9.1, 2.1 Hz, 2H), 6.41 (d, *J* = 10.9 Hz, 2H), 5.87 (ddd, *J* = 17.2, 10.0, 7.3 Hz, 2H), 5.07 (d, *J* = 17.2 Hz, 2H), 5.05 (d, *J* = 10.0 Hz, 2H), 3.87 (q, *J* = 9.2 Hz, 2H) 3.83 (s, 6H), 3.16 (dd, *J* = 13.4, 10.2 Hz, 2H), 2.84−2.89 (m, 4H), 2.59−2.65 (m, 2H), 2.30−2.33 (m, 2H), 1.81−1.83 (m, 2H), 1.70−1.75 (m, 4H), 1.33−1.38 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.5, 147.6, 145.1, 141.5, 140.4, 139.1, 132.1, 127.9, 122.2, 119.9, 119.5, 115.1, 100.2, 61.6, 57.1, 56.9, 55.8, 41.4, 39.4, 27.7, 27.3, 25.2. HR-MS (ESI-TOF) *m*/*z* calculated for $[C_{44}H_{48}N_{10}O_2+H]^+$: 749.4034; found: 749.4031

1,1′-Di((8*R*,9*R*)-10,11-dihydro-6′-methoxycinchonan-9-yl)-4,4′-bi-1,2,3-triazole (*e*DHQD-2). Following the general procedure, starting from 9*R*-azido-9-deoxy-10,11-dihydroquinidine (***e*DHQD-1**, 828 mg, 2.35 mmol), 628 mg of product (78%) was obtained after chromatography ($CHCl_3$/MeOH 15:1 v/v) as white solid. $[\alpha]_D^{25} = +258$ (*c* 1.04, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (d, *J* = 4.6 Hz, 2H), 8.00 (d, *J* = 9.2 Hz, 2H), 7.98 (s, 2H), 7.50 (d, *J* = 4.6 Hz, 2H), 7.48 (d *J* = 2.6 Hz, 2H), 7.34 (dd, *J* = 9.2, 2.6 Hz, 2H), 6.43 (d, *J* = 11.0 Hz, 2H), 3.91 (s, 6H), 3.78−3.83 (m, 2H), 2.92 (dd, *J* = 14.2, 9.3 Hz, 2H), 2.85−2.90 (m, 2H), 2.78−2.83 (m, 2H), 2.70−2.74 (m, 2H), 1.60−1.65 (m, 4H), 1.48−1.53 (m, 2H), 1.41−1.46 (m, 4H), 1.35−1.40 (m, 2H), 1.27−1.34 (m, 2H), 1.16−1.21 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8, 147.5, 145.1, 140.1, 139.4, 132.2, 128.2, 122.5, 119.4 (2C overlapped), 100.6, 59.9, 58.4, 55.8, 49.64, 49.59, 37.5, 27.5, 26.4, 26.1, 26.0, 12.1. HR-MS (ESI-TOF) *m*/*z* calculated for $[C_{44}H_{52}N_{10}O_2+H]^+$: 753.4347; found: 753.4354

1,1′-Di((8*R*,9*S*)-10,11-dihydro-6′-methoxycinchonan-9-yl)-4,4′-bi-1,2,3-triazole (DHQD-2). Following the general procedure, starting from 9*S*-azido-9-deoxy-10,11-dihydroquinidine (**DHQD-1**, 500 mg, 1.42 mmol), 251 mg of product (47%) was obtained after chromatography ($CHCl_3$/MeOH 15:1 v/v) as white solid. $[\alpha]_D^{25} = -93$ (*c* 1.06, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (d, *J* = 4.6 Hz, 2H), 7.94 (d, *J* = 9.1 Hz, 2H), 7.74 (s, 2H), 7.61 (d, *J* = 4.5 Hz, 2H), 7.32 (d *J* = 2.0 Hz, 2H), 7.25 (dd, *J* = 9.1, 2.0 Hz, 2H), 6.39 (d, *J* = 11.1 Hz, 2H), 3.74−3.90 (m, 2H), 3.83 (s, 6H), 3.05 (t, *J* = 11.6 Hz, 2H), 2.90−2.78 (m, 4H), 2.41 (d, *J* = 8.7 Hz, 2H), 1.69 (s, 2H), 1.64 (t, *J* = 9.4 Hz, 2H), 1.61−1.51 (m, 4H), 1.48−1.38 (m, 6H), 1.16−1.09 (m, 2H), 0.86 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 147.5, 145.0, 140.3, 139.5, 132.0, 127.9, 122.1, 119.48, 119.44, 100.4, 60.9, 57.3, 55.7, 49.9, 49.2, 37.4, 27.1, 25.7, 25.4, 24.2, 11.9. HR-MS (ESI-TOF) *m*/*z* calculated for $[C_{44}H_{52}N_{10}O_2+H]^+$: 753.4347; found: 753.4362

1,1′-Di((8*S*,9*S*)-cinchonan-9-yl)-4,4′-bi-1,2,3-triazole (*e*CD-2). Following the general procedure, starting from 9*S*-azido-9-deoxy-cinchonidine (***e*CD-1**, 511 mg, 1.60 mmol), 400 mg of product (67%) was obtained after chromatography ($CHCl_3$/MeOH 20:1 v/v) as white solid. $[\alpha]_D^{25} = -107$ (*c* 0.95, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$, 318 K) δ 8.93 (d, *J* = 4.4 Hz, 2H), 8.29 (d, *J* = 8.5 Hz, 2H), 8.12 (d, *J* = 8.5 Hz, 2H), 8.07 (s, 2H), 7.67−7.70 (m, 2H), 7.54−7.58 (m, 4H), 6.52 (d, *J* = 11.4 Hz, 2H), 5.86 (ddd, *J* = 17.2, 10.6, 7.3 Hz, 2H), 5.03−5.06 (m, 4H), 3.86−3.91 (m, 2H), 3.31−3.37 (m, 2H), 3.12 (dd, *J* = 13.9, 10.5 Hz, 2H), 2.65−2.73 (m, 4H), 2.28 (br. s, 2H), 1.77−1.81 (m, 2H), 1.72 (br. s, 2H), 1.52−1.60 (m, 4H), 0.84 (dd, *J* = 13.3, 7.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.2, 148.9, 141.5, 140.8, 140.0, 130.8, 129.8, 127.9, 127.0, 122.6, 119.6, 119.4, 114.9, 60.1, 58.4, 56.1, 41.1, 39.3, 27.8, 27.7, 27.3. HR-MS (ESI-TOF) *m*/*z* calculated for $[C_{42}H_{44}N_{10}+H]^+$: 689.3823; found: 689.3823

1,1′-Di((8*R*,9*S*)-10,11-dihydrocinchonan-9-yl)-4,4′-bi-1,2,3-triazole (DHCN-2). Following the general procedure, starting from 9*S*-azido-9-deoxy-10,11-dihydrocinchonine (**DHCN-1**, 181 mg, 0.56 mmol), 42 mg of product (22%) was obtained after chromatography ($CHCl_3$/MeOH 20:1 v/v) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.00 (d, *J* = 4.4 Hz, 2H), 8.19 (d, *J* = 8.6 Hz, 2H), 8.11 (d, *J*

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= 8.5 Hz, 2H), 7.89 (s, 2H), 7.71 (d, J = 4.4 Hz, 2H), 7.67 (t, J = 7.7 Hz, 2H), 7.54 (t, J = 7.7 Hz, 2H), 6.53 (d, J = 10.9 Hz, 2H), 3.91−3.96 (m, 2H), 3.03 (t, J = 11.4 Hz, 2H), 2.79−2.89 (m, 4H), 2.40−2.44 (m, 2H), 1.72 (br. s, 2H), 1.20−1.70 (m, 12H), 0.85−0.93 (m, 8H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.3, 149.0, 141.7, 140.2, 130.8, 129.5, 127.6, 126.9, 122.2, 119.8, 119.3, 60.6, 57.7, 50.0, 49.4, 37.5, 29.8, 27.2, 25.8, 25.6, 24.6, 12.0. HR-MS (ESI-TOF) m/z calculated for $[C_{42}H_{48}N_{10}+H]^+$: 693.4136; found: 693.4130

1,2-Di(1-((8*S*,9*S*)-6′-methoxycinchonan-9-yl)-1,2,3-triazol-4-yl)benzene (*e*QN-3). 9-*Epi*-9-azido-9-deoxy-quinine (***e*QN-1**, 1.40 g, 4.01 mmol) and 1,2-bis(trimethylsilylethynyl)-benzene (515 mg, 1.91 mmol, 0.477 equiv) were suspended in a mixture of *tert*-butanol (20 mL) and water (10 mL). Pyridine (0.4 mL) was added followed by $CuSO_4{\cdot}5H_2O$ (338 mg), sodium ascorbate (0.84 g), and potassium carbonate (1.06 g). After addition the mixture turned into brown suspension. After 2 days of stirring, aqueous ammonia (25% soln., 1 mL) was added and the mixture stirred for another 3 h. Solution of sodium sulfide (satd. aqueous, 0.2 mL) was added, the mixture was extracted with CH_2Cl_2 and passed through a pad of silica gel and washed with chloroform. Subsequent purification on a silica gel column ($CHCl_3$/MeOH 15:1 v/v) gave 1.30 g (83%) of brown amorphous solid. mp 141−148 °C (dec); $[\alpha]_D^{25}$ = −160 (c 0.091, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (d, J = 4.5 Hz, 2H), 8.04 (d, J = 9.2 Hz, 2H), 7.98 (s, 2H), 7.49 (s, 2H), 7.63 (dd, J = 5.8, 3.4 Hz, 2H), 7.51 (br., 2H), 7.40 (dd, J = 9.1, 2.6 Hz, 2H), 7.30 (dd, J = 5.8, 3.4 Hz, 2H), 6.31 (br., 2H), 5.84 (ddd, J = 17.4, 10.0, 7.2 Hz, 2H), 5.04−5.07 (m, 4H), 3.95 (s, 6H), 3.81−3.90 (m, 2H), 3.23−3.30 (m, 2H), 2.97 (dd, J = 13.7, 10.2 Hz, 2H), 2.64−2.71 (m, 2H), 2.54−2.59 (m, 2H), 2.23−2.27 (m, 2H), 1.69−1.75 (m, 4H), 1.50−1.60 (m, 4H), 0.83−0.87 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 147.5, 146.3, 145.0, 141.3, 139.6, 132.2, 130.4, 129.2, 128.2, 128.0, 122.4, 122.1, 119.9, 114.8, 101.0, 60.4, 58.4, 55.9, 55.8, 41.1, 39.2, 27.8, 27.6, 26.8. HR-MS (ESI-TOF) m/z calculated for $[C_{50}H_{52}N_{10}O_2+H]^+$: 825.4347; found: 825.4339

2,6-Di(1-((8*S*,9*S*)-6′-methoxycinchonan-9-yl)-1,2,3-triazol-4-yl)pyridine (*e*QN-4). 2,6-Diethynylpyridine[19] (134 mg, 1.06 mmol, 0.49 equiv) and 9-*epi*-9-azido-9-deoxy-quinine (***e*QN-1**, 749 mg, 2.14 mmol) were dissolved in THF (10 mL), CuI (12 mg) was added, and the mixture was stirred for 48 h. Then the mixture was diluted with CH_2Cl_2 and a saturated aqueous solution of Na_2S (2 drops) was added. The mixture was washed with water, extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated. The mixture was filtered through silica gel ($CHCl_3$/MeOH 20:1). Obtained 883 mg >99%. mp 205−215 °C. $[\alpha]_D^{22}$ = −213 (c 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (br., 2H), 7.94−8.05 (m, 6H), 7.65 (br., 1H), 7.49 (s, 2H), 7.38 (br., 2H), 7.32 (d, J = 8.9 Hz, 2H), 6.41 (br., 2H), 5.81−5.87 (m, 2H), 5.08 (d, J = 10.5 Hz, 2H), 5.04 (d, J = 17.1 Hz, 2H), 3.92 (s, 6H), 3.79 (br., 2H), 3.42 (br., 2H), 2.99 (br., 2H), 2.47−2.68 (m, 4H), 2.24 (br., 2H), 1.89 (br., 2H), 1.72 (s, 2H), 1.55 (br., 4H), 0.84 (br., 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8, 150.1, 148.0, 147.3, 145.0, 141.4, 138.6, 137.7, 131.9, 128.3, 122.6, 120.6, 119.6, 119.3, 114.9, 100.8, 60.9, 57.9, 55.97, 55.94, 41.0, 39.1, 27.79, 27.71, 27.69. HR-MS (ESI-TOF) m/z calculated for $[C_{49}H_{51}N_{11}O_2+H]^+$: 826.4300; found: 826.4291

2,4-Di(1-((8*S*,9*S*)-6′-methoxycinchonan-9-yl)-1,2,3-triazol-4-yl)thiophene (*e*QN-5). 9-*Epi*-9-azido-9-deoxy-quinine (***e*QN-1** 1.86 g, 5.33 mmol) and 2,5-bis(trimethylsilylethynyl)-thiophene[18] (0.574 g, 2.08 mmol, 0.39 equiv) were suspended in a mixture of *tert*-butanol (25 mL) and water (15 mL). Pyridine (0.4 mL) was added followed by $CuSO_4{\cdot}5H_2O$ (382 mg), sodium ascorbate (0.84 g), and potassium carbonate (1.43 g). After addition the mixture turned into orange suspension, and after 2 days became yellowish-gray. Then aqueous ammonia (25% soln., 1 mL) was added and the mixture stirred for another 3 h. Solution of sodium sulfide (satd. aqueous, 0.2 mL) was added, and after 5 min the mixture passed through a pad of silica gel and was washed with $CHCl_3$/MeOH (10:1 v/v, 50 mL), was evaporated, and was purified on silica gel ($CHCl_3$/MeOH 20:1 v/v). A portion of crude material was purified by crystallization in Soxhlet apparatus from methanol. A total of 1.78 g (99%) of white crystalline product was obtained. mp 274−276 °C (dec, MeOH). $[\alpha]_D^{25}$ = −288 (c 0.90, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (d, J = 4.6 Hz, 2H), 8.00 (d, J = 9.2 Hz, 2H), 7.60 (br. s, 2H), 7.53 (d, J = 2.7 Hz, 2H), 7.51 (d, J = 4.6 Hz, 2H), 7.34 (dd, J = 9.2, 2.6 Hz, 2H), 7.15 (s, 2H), 6.42 (d, J = 11.1 Hz, 2H), 5.88 (ddd, J = 17.4, 9.9, 7.0 Hz, 2H), 5.04−5.07 (m, 4H), 3.91−3.96 (m, 2H), 3.91 (s, 6H), 3.39−3.45 (m, 2H), 3.15 (dd, J = 14.0, 10.2 Hz, 2H), 2.68−2.75 (m, 4H), 2.27−2.32 (m, 2H), 1.87−1.91 (m, 2H), 1.73−1.76 (m, 2H), 1.53−1.63 (m, 4H), 0.85−0.90 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8, 147.4, 145.1, 142.6, 141.4, 139.0, 132.4, 132.1, 128.3, 124.5, 122.5, 119.5, 117.8, 114.9, 100.9, 60.9, 58.0, 56.1, 55.9, 41.1, 39.2, 27.74, 27.73, 27.6. HR-MS (ESI-TOF) m/z calculated for $[C_{48}H_{50}N_{10}O_2S+H]^+$: 831.3912; found: 831.3902

1,8-Di(1-((8*S*,9*S*)-6′-methoxycinchonan-9-yl)-1,2,3-triazol-4-yl)naphthalene (*e*QN-6). 9-*Epi*-azido-9-deoxy-quinine (***e*QN-1** 973 mg, 2.78 mmol, 2.04 equiv) and 1,8-bis(trimethylsilylethynyl)-naphthalene[19] (435 mg, 1.36 mmol) were suspended in a mixture of *tert*-butanol (15 mL) and water (7 mL). Pyridine (0.3 mL) was added followed by $CuSO_4{\cdot}5H_2O$ (221 mg), sodium ascorbate (0.62 g), and potassium carbonate (0.83 g). After 2 days of stirring, aqueous ammonia (25% soln., 1 mL) was added and the mixture stirred for another 3 h. Solution of Na_2S (satd. aqueous, 0.2 mL) was added, the mixture was extracted with CH_2Cl_2, passed through a pad of silica gel, washed with chloroform, and evaporated to give 1.15 g of crude material. Subsequent purification on a silica gel column ($CHCl_3$/MeOH 15:1 v/v) gave 1.10 g of off-white amorphous solid (92%). $[\alpha]_D^{25}$ = −43 (c 1.14, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (br., 2H), 7.87−7.82 (m, 4H), 7.68 (br., 2H), 7.55−7.58 (m, 2H), 7.37 (br., 2H), 7.28 (br., 2H), 7.20 (br., 2H), 6.67 (br., 2H), 6.11 (br., 2H), 5.49 (br., 2H), 4.76−4.83 (m, 4H), 4.00 (s, 6H), 3.12 (br., 2H), 2.77−2.95 (m, 4H), 2.43 (br., 2H), 2.27 (br., 2H), 2.03 (br., 2H), 1.44 (s, 2H), 1.37 (br. 4H) 1.06 (br., 2H), 0.56 (br., 2H). ^{13}C NMR (151 MHz, $CDCl_3$, 315 K) δ 158.4, 147.8, 147.0, 144.3, 141.1, 139.3, 135.1, 132.0, 131.0, 129.6, 128.9, 128.2, 127.1, 125.6, 124.1, 121.7, 120.2, 114.5, 100.6, 59.6, 59.3, 55.7, 55.6, 40.8, 39.1, 27.8, 27.4, 25.5. (1 C-sp^2 not observed due to overlap). HR-MS (ESI-TOF) m/z calculated for $[C_{54}H_{54}N_{10}O_2+H]^+$: 875.4504; found: 875.4513

(8*S*,9*S*)-6′-Methoxy-9-(4-trimethylsilyl-1,2,3-triazol-1-yl)-cinchonan (*e*QN-7). To a solution of 9-*epi*-azido-9-deoxy-quinine (***e*QN-1** 1.38 g, 3.97 mmol) in MeOH (20 mL) were added water (9 mL), TMS-acetylene (1 mL, 7.08 mmol, 1.78 equiv), copper sulfate pentahydrate (36 mg), and sodium ascorbate (0.3 g). The mixture was stirred at room temperature for 24 h and then saturated Na_2S solution was added (2 drops). The mixture was concentrated *in vacuo*, the residue was suspended in CH_2Cl_2, was dried over $MgSO_4$, and was passed through a plug of silica gel. On evaporation 1.74 g of pure ***e*QN-7** was obtained (98%) as white slowly crystallizing solid. mp 180−182 °C; $[\alpha]_D^{23}$ = −115 (c 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.56 (br., 1H), 7.51 (d, J = 4.5 Hz, 1H), 7.43 (s, 1H), 7.39 (dd, J = 9.3, 2.7 Hz, 1H), 6.60 (br., 1H), 5.92 (ddd, J = 17.4, 10.0, 7.0 Hz, 1H), 5.10−5.13 (m, 2H), 4.07 (br., 1H), 3.97 (s, 3H), 3.37−3.43 (m, 1H), 3.24 (dd, J = 13.8, 10.5 Hz, 1H), 2.78−2.91 (m, 2H), 2.39 (br. s, 1H), 1.93−1.98 (m, 1H), 1.82 (br. s, 1H), 1.59−1.64 (m, 2H), 0.98−1.06 (br., 1H), 0.22 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 147.4, 146.4, 145.0, 141.5, 139.8, 131.9, 128.3, 127.3, 122.4, 119.5, 114.7, 100.9, 60.1, 58.1, 56.0, 55.8, 41.0, 39.2, 27.79, 27.73, 27.5, −1.0. HR-MS (ESI-TOF) m/z calculated for $[C_{25}H_{33}N_5OSi+H]^+$: 448.2527; found: 448.2511

(8*S*,9*S*)-6′-Methoxy-9-(1,2,3-triazol-1-yl)cinchonan (*e*QN-8). In a polypropylene tube TMS-protected compound ***e*QN-7** (100 mg, 0.22 mmol) was dissolved in a solution of hydrofluoric acid (prepared by dissolving 0.2 mL of 40% aqueous HF in 2 mL of methanol). After 4 h aqueous sodium bicarbonate was added and the mixture extracted with CH_2Cl_2. The combined organic phases were dried and evaporated to yield 75 mg (90%) pure ***e*QN-8** as an off-white solid. mp 167−169 °C; $[\alpha]_D^{25}$ = −34 (c 1.09, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (d, J = 4.5 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.59 (d, J = 0.7 Hz, 1H), 7.51 (br., 2H), 7.49 (d, J = 4.5 Hz, 1H), 7.36 (dd, J = 9.2, 2.6 Hz, 1H), 6.50 (d, J = 11.1 Hz, 1H), 5.91 (ddd, J = 17.3, 10.0, 7.0 Hz, 1H), 5.07−5.10 (m, 2H), 3.94−3.99 (m,

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1H), 3.93 (s, 3H), 3.43−3.49 (m, 1H), 3.21 (dd, J = 14.1, 10.2 Hz, 1H), 2.72−2.80 (m, 2H), 2.32−2.37 (m, 1H), 1.89−1.95 (m, 1H), 1.79 (sext, J = 3.0 Hz, 1H), 1.57−1.67 (m, 2H), 0.92−0.96 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.8, 147.5, 145.2, 141.4, 139.2, 134.0, 132.2, 128.3, 122.5, 122.1, 119.4, 115.0, 100.9, 60.7, 58.2, 56.2, 55.9, 41.2, 39.2, 27.79, 27.77, 27.65. HR-MS (ESI-TOF) m/z calculated for $[C_{22}H_{25}N_5O+H]^+$: 376.2132; found: 376.2147

General Procedure for Asymmetric Michael Addition−Cyclization Reaction. Ligand (10 mol%, 0.025 mmol) and copper(II) triflate (9.0 mg, 0.025 mmol, 10 mol%) were suspended in dichloromethane (1.0 mL) and the resulting light blue quasi-homogeneous solution was stirred for 1.5 h at 20 °C. Michael acceptor **9** (0.25 mmol, 1.0 equiv) was added and the mixture was stirred for another 0.5 h at 20 °C and the color turned light yellow to green. Finally, dimedone or 1,3-cyclohexanedione (0.25 mmol, 1.0 equiv) in 0.5 mL of dichloromethane were added, resulting in a homogeneous solution and color change to deep green or reddish. In case of 1,3-cyclohexanedione a precipitate appears after a few hours. The reaction was run for 48 h at 17−20 °C, then diluted by AcOEt (5 mL), and filtered through a pad of silica gel eluting with a total volume of 150 mL AcOEt. The filtrate was evaporated *in vacuo*. Crude products were analyzed by HPLC. Pure samples were obtained after chromatography (silica gel, 35−40 g, hexanes/AcOEt 3:1 to 2:1, v/v) as colorless oils that transformed to amorphous solids. The absolute configuration of products were determined by comparison of the sign of the $[\alpha]_D$ and order of elution in HPLC with the literature data (For the details, see SI).[25]

Ethyl 4-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)-4-(4-methoxy-phenyl)-2-oxobutyrate (10). Following the general procedure using ***e*QN-2** as ligand, 52 mg (62%) of colorless oil was obtained. The enantiomeric excess was determined by analytical HPLC (Chiralpak AD column, 70:30 hexanes:isopropanol, 0.7 mL/min, λ 254 nm) t_r (4*R*) = 6.7 min, t_r (4*S*) = 9.7 min, ee =73%: $[\alpha]_D$ = −7.0 (c 0.6, CH_2Cl_2).

Ethyl 2-Hydroxy-3,4,5,6,7,8-hexahydro-5-oxo-4-phenyl-2H-chromene-2-carboxylate (11). Following general procedure using ***e*QN-2** as ligand, 58 mg (73%) of colorless oil was obtained. The enantiomeric excess was determined by analytical HPLC (Chiralpak AD column, 80:20 hexanes:isopropanol, 0.75 mL/min, λ 254 nm) t_r (4*R*) = 9.9 min, t_r (4*S*) = 13.3 min, ee =82%: $[\alpha]_D$ = +17.5 (c 1.0, CH_2Cl_2).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01403.

Supporting tables, ^{1}H and ^{13}C NMR spectra for new compounds, chromatograms for **10** and **11**, and computational details for ***e*QN-2** (PDF)

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Notes

The authors declare no competing financial interest.

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