Table 2. Biological activity (IC_{50}) for HIV-1 RT inhibition, L1210 and HCT116 cytotoxic activity.

Compound	HIV-1 RT[a] [μM]	L1210[b] [nM]	HCT116[c] [nM]
1	0.6	0.3	1
2	0.9	2	7
3	0.3	> 100	> 100
4	6	0.008	0.3
5	3	30	30
6	0.4	> 100	> 100
11	0.7	2	6
13	0.9	> 100	> 100
14	0.8	7	n.d.[d]
Sandramycin	2	0.001	0.007

[a] HIV-1 reverse transcriptase inhibition. [b] L1210 mouse leukemia cytotoxic assay. [c] Human colon carcinoma assay. [d] n.d. = not determined.

possessing the unnatural (*R,R*)-2-methylcyclopropane carboxylic acid substituent proved to be only slightly less potent than natural quinoxapeptin A (**1**) in both the HIV-1 RT and cytotoxic assays. In addition, the quinoxapeptins displayed activity trends analogous to those observed with the luzopeptins with the important exception that the RT inhibition was more potent and the cytotoxic activity less potent enhancing the selective RT inhibition observed with the quinoxapeptins. The comparison of the quinoxapeptin derivative **14** with luzopeptin A (**4**) is instructive in this regard, where **14** was nearly 10-fold more potent against HIV-1 RT and 1000 times less potent in the L1210 cytotoxic assay. The HIV-1 RT inhibition follows the trend of quinoxapeptin C > A analogous to the luzopeptin C > B > A potency with the L-Htp free alcohols being the most active agents in each series. A reverse potency order was observed in the cycotoxic assays with quinoxapeptin A ≫ C and luzopeptin A > B ≫ C with the L-Htp free alcohols being inactive. Thus, the synthetic precursor **3** (quinoxapeptin C), which has not yet been disclosed as a natural product, exhibits the most potent HIV-1 RT inhibition in the series and lacks a dose-limiting in vitro cytotoxic activity making it the most attractive member of the series examined to date.

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[7] EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole, SES = 2-(trimethylsilyl)ethylsulfonyl, TBS = *tert*-butyldimethylsilyl.

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Rhodium(I)-Catalyzed [2+2+2] Cycloadditions with N-Functionalized 1-Alkynylamides: A Conceptually New Strategy for the Regiospecific Synthesis of Substituted Indolines**

Bernhard Witulski* and Thomas Stengel

Stereoselective syntheses of multifunctionalized indoles and indolines (2,3-dihydroindoles) are a continuous challenge because of the enormous relevance of this class of compounds in the fields of natural products, pharmaceuticals, and drug-related targets.[1] Substructures of highly functionalized indoles are found in numerous natural products and pharmaceutically active compounds, for instance in the ergot alkaloids,[2] the telocidines,[3] the diazonamides[4] as well as in *N*-methylwelwitindolinone C,[5] an indolinone alkaloid that

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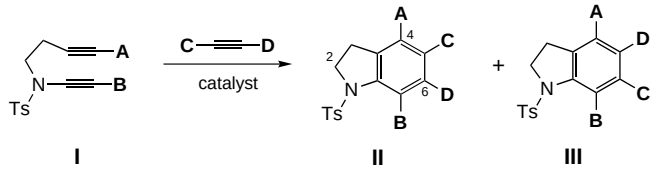
reverses the multiple-drug-resistance of vinblastine-resistant adenocarcinoma cells.

While the functionalization of the indole or indoline ring system through reactions with electrophiles is often limited to the electronically activated (3-), 5-, and 7-positions, the regioselective functionalization of the 4-position—most significant for the synthesis of various natural products and pharmaceuticals—is in many cases difficult.[1, 6] Syntheses of multifunctionalized indoles and indolines based on annulation strategies[1, 7] are equally laborious since they may be encumbered with the disadvantages of moderately pronounced regioselectivities and multistep syntheses of the corresponding highly functionalized benzene precursors.

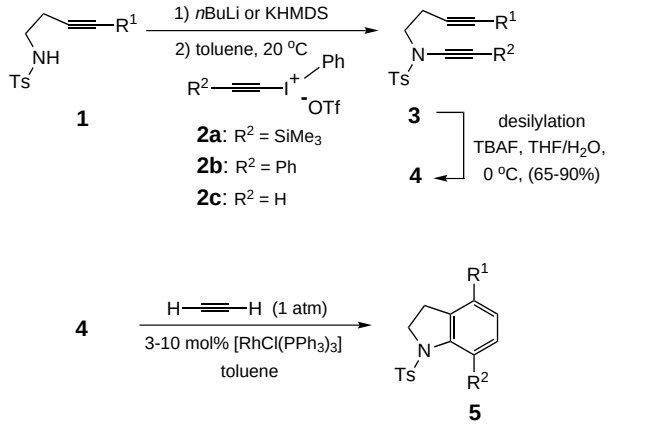
Here we report a conceptually new strategy for the synthesis of multifunctionalized indolines that is based on transition metal catalyzed [2+2+2] cycloadditions[8] which utilize our recently reported N-functionalized and electronically tunable 1-alkynylamides as key building blocks.[9]

The design of this new indoline synthesis is based on the use of *N*-(3-butynyl)-1-alkynylamides of type **I** in rhodium(I)-catalyzed cyclotrimerizations[10] with differently substituted monoalkynes; hence it should allow the regiospecific introduction of functional groups into the 4- *or* 7-position as well as into the 4- *and* 7-position of the indoline moiety. However, if asymmetrically substituted monoalkynes are used as cycloaddition partners, two regioisomeric products should be expected (Scheme 1).



Scheme 1. Strategy for the synthesis of multifunctionalized indolines by [2+2+2] cycloadditions. Ts = *p*-toluenesulfonyl.

The synthesis of the diynes **3** and **4** needed for the alkyne cyclotrimerization studies relied on our recently developed approach to N-functionalized 1-alkynylamides (Scheme 2 and Table 1).[9] The diynes **3** are available in yields of 45–80% after deprotonation of the amides **1**[11] with *n*-butyllithium or potassium hexamethyldisilazide (KHMDS), followed by the addition of the alkynyliodonium salts[12] **2a–c** in toluene. In addition to the previously utilized **2a** ($R^2 = SiMe_3$), the alkynyliodonium salt **2b** (R = Ph), and the parent compound **2c** (R = H) could be applied as reagents for an efficient ethynylation process (entries 7–9, and 11 in Table 1).[13] Desilylation of **3** with tetrabutylammonium fluoride (TBAF) in wet THF gave the terminal diynes **4** in yields of between 65 and 90%.



Scheme 2. Synthesis of the *N*-(3-butynyl)-1-alkynylamides **3** and **4** and their rhodium(I)-catalyzed cyclotrimerizations with acetylene. Tf = trifluoromethanesulfonyl.

Table 1. Products of the ethynylation of **1** with the alkynyliodonium salts **2a–c**.

Entry	**1**	R^1[a]	**2**	R^2	**3**	Yield [%][b]
1	**1a**	$SiMe_3$	**2a**	$SiMe_3$	**3a**	69
2	**1b**	$(CH_2)_2OTBDMS$	**2a**	$SiMe_3$	**3b**	80
3	**1c**	$(CH_2)_2OBzl$	**2a**	$SiMe_3$	**3c**	66
4	**1d**	$(CH_2)_2OTHP$	**2a**	$SiMe_3$	**3d**	43
5	**1e**	$(CH_2)_2NHTs$	**2a**	$SiMe_3$	**3e**	28
6	**1f**	Ph	**2a**	$SiMe_3$	**3f**	72
7	**1g**	Ph	**2c**	H	**3g**	85
8	**1h**	CO_2Me	**2c**	H	**3h**	35
9	**1i**	H	**2b**	Ph	**3i**	50
10	**1j**	H	**2a**	$SiMe_3$	**3j**	64
11	**1k**	$(CH_2)_2OBzl$	**2b**	Ph	**3k**	55
12	**1l**	CH_2OTHP	**2a**	$SiMe_3$	**3l**	60

[a] TBDMS = *tert*-butyldimethylsilyl; THP = tetrahydropyranyl. [b] Yields obtained after column chromatography.

Significantly, the unsubstituted diyne **4a** and its monosubstituted derivatives **4b–e** as well as **3g** and **3h** were particularly suitable substrates for rhodium(I)-catalyzed [2+2+2] cycloadditions with monoalkynes. Crossed cyclotrimerizations of **4a–e** and **3g** (0.01–0.03 M) with acetylene (1 atm) already occur at temperatures between 0 and 20 °C in toluene with 3–5 mol% of $[RhCl(PPh_3)_3]$ as catalyst. On the contrary, the cyclotrimerization of acetylene with the diyne **3h**, which bears an electron-withdrawing alkyne substituent, required a temperature of 110 °C to complete the reaction. The resulting indolines **5a–h** were obtained in yields of 43–91% after isolation by column chromatography on silica gel (Table 2).[14] Apart from toluene, dichloromethane, ethanol, and trifluoroethanol could be used as solvents.[15]

In addition to the regiospecific introduction of substituents into the 4-position of the indoline core by rhodium(I) catalysis, those of both the 7-position and the 4- *and* 7-position succeeded in yields of 68–95% (Table 3).[14] However, in these cases cyclotrimerizations with acetylene go to completion only when carried out at 100 °C in a sealed Schlenk tube and with catalyst loadings of 5–10 mol% $[RhCl(PPh_3)_3]$. Evidently a substituent at the *N*-1-alkynylamide moiety causes a decrease in effectiveness of the cycloadditions with acetylene.

Initial results regarding the quest for a regioselective functionalization of the 5- and 6-position of the indoline core were obtained by cyclotrimerization studies with monosubstituted alkynes. Rhodium(I)-catalyzed [2+2+2] cycloadditions in toluene with **4a** and the alkynols **6a–c** (5 equivalents) yielded the indolines **7a**,**b**, **8a**,**b**, and **9a**,**b**, respectively,

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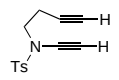
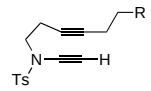
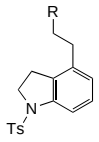
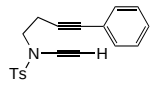
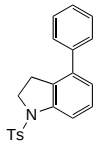
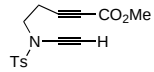
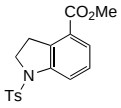
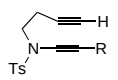
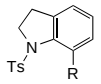
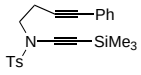
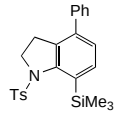
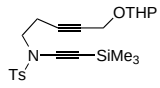
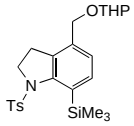
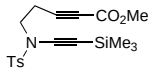
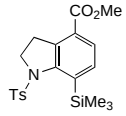
Table 2. Rhodium(I)-catalyzed [2+2+2] cycloadditions with acetylene for the regiospecific synthesis of indolines with functional groups in the 4-position.

Entry	Diyne	T [°C]	t [h]	Product (yield [%])[a]
				
1	**4a**	20	0.5	**5a** (91)
				
2	**4b**: R = OH	0	5	**5b**: R = OH (70)
3	**4c**: R = OBzl	20	2	**5c**: R = OBzl (55)
4	**4d**: R = OTHP	20	2	**5d**: R = OTHP (57)
5	**4e**: R = NHTs	20	2	**5e**: R = NHTs (65)
				
6	**3g**	20	3	**5g** (65)
				
7[b]	**3h**	110	2	**5h** (43)

[a] All reactions were carried out in acetylene-saturated toluene. Yields refer to products obtained after column chromatography. [b] The reaction was carried out in a sealed Schlenk flask.

Table 3. Rhodium(I)-catalyzed [2+2+2] cycloadditions with acetylene for the regiospecific synthesis of indolines with functional groups in the 7-, as well as in the 4- *and* 7-position.

Entry	Diyne	T [°C]	t [h]	Product (yield [%])[a]
				
1	**3i**: R = Ph	110	24	**5i**: R = Ph (85)
2	**3j**: R = $SiMe_3$	110	18	**5j**: R = $SiMe_3$ (68)
				
3	**3f**	110	18	**5k** (93)
				
4	**3d**	110	18	**5l** (95)
				
5[b]	**3m**	110	18	**5m** (92)

[a] All reactions were carried out in acetylene-saturated toluene. Yields refer to products obtained after column chromatography. [b] Compound **3m** was obtained by carboxymethylation of **3j** with cyanoformic acid methyl ester.

without any preference for a particular regioisomer (entries 1–3 in Table 4). On the contrary, cyclotrimerizations of the alkynol **6b** with the differently substituted diynes **3i** and **3j** were accompanied by a substantial *meta*-selectivity, presumably caused by steric interactions of the diyne and monoyne substituents (entry 4 and 5 in Table 4).[16]

Furthermore, the simultaneous introduction of three or four different substituents into the indoline ring system could be achieved with this novel strategy as demonstrated by the cyclotrimerization of diyne **3k** with the monoalkynes **6b** and **13**. Surprisingly a pronounced selectivity (**12a**:**12b** = 20:1) was accomplished in the case of the cycloaddition of the diyne **3k** with **6b**.[17]

Even though the observed regioselectivities with respect to the functionalization of the 5- and the 6-positions need further investigations regarding the influence of the substitution pattern and the catalyst, the following can be summarized: the strategy outlined herein for the synthesis of multifunctionalized indolines by rhodium(I)-catalyzed [2+2+2] cycloadditions is compatible with a rich variety of substituents and a pronounced structural diversity with regard to the obtainable substitution pattern. The flexibility and efficiency of this conceptually novel indoline synthesis, which is also based on the efficient access to the diynes **3** and **4** through a direct ethynylation process with the alkynyliodonium salts **2a–c**, are illustrated by the examples in the Tables 2–4. The cyclotrimerizations are relatively insensitive towards steric hindrance (acceptance of hydrogen to trimethylsilyl groups), electronic effects (compatibility of electron-withdrawing, electron-donating, and conjugating substituents in the acetylene components), and functional group diversity (acceptance of alcohol, ether, amide, and ester groups). The application of terminal rather than non-terminal alkynes has only minor effects with respect to reactivity and overall efficiency, although the utilization of non-terminal diynes is sometimes accompanied by higher yields (entries 6 and 7 in Table 2 and entries 3 and 5 in Table 3, respectively). In addition to the regiospecific functionalization of the 4- *or* the 7-position as well as the 4- *and* 7-positions, the simultaneous introduction of one to four substituents into the indoline core is possible with one strategy.

Experimental Section

5b: $[RhCl(PPh_3)_3]$ (9 mg, 0.0097 mmol) was added to a solution of **4b** (64 mg, 0.22 mmol) in dry toluene (15 mL) saturated with acetylene (1 atm) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C in an atmosphere of acetylene (1 atm). The solvent was evaporated and the resulting crude product purified by column chromatography (silica gel, hexanes:diethyl ether = 1:1 (v/v)) to afford indoline **5b** (49 mg, 0.15 mmol; 70 %) as colorless plates. M.p. 101–102 °C (hexanes/diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.67 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 7.15 (t, J = 7.9 Hz, 1H), 6.84 (d, J = 7.4 Hz, 1H), 3.91 (t, J = 8.4 Hz, 2H), 3.75 ("d", $J \approx$ 4.6 Hz, 2H), 2.87 (t, J = 8.4 Hz, 2H), 2.71 (t, J = 6.7 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 144.04 (s), 142.04 (s), 135.16 (s), 133.93 (s), 130.86 (s), 129.61 (d), 128.06 (d), 127.30 (d), 124.23 (d), 113.03 (d), 62.28 (t), 49.73 (t), 36.08 (t), 26.57 (t),

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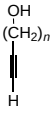
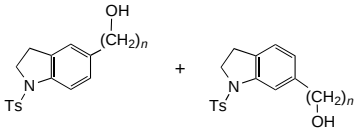
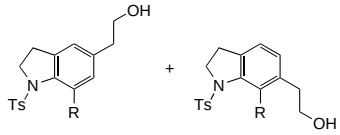
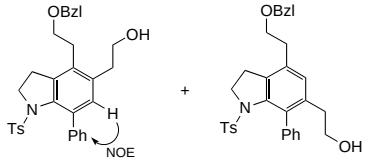
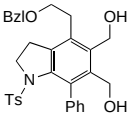
Table 4. Regioselectivity of rhodium(I)-catalyzed cyclotrimerizations.

Entry	Diyne	Monoalkyne[a]	T [°C]	Products (isomer ratio[b])	Yield [%][c]
					
1	**4a**	**6a**: $n=1$	20	**7a** + **7b** (1.3:1)	60
2	**4a**	**6b**: $n=2$	20	**8a** + **8b** (1.0:1)	85
3	**4a**	**6c**: $n=3$	20	**9a** + **9b** (1.0:1)	63
					
4	**3i**	**6b**	110	R = Ph: **10a** + **10b** (10:1)	68
5	**3j**	**6b**	110	R = $SiMe_3$: **11a** + **11b** (2.7:1)	60
					
6	**3k**	**6b**	110	**12a** + **12b** (20:1)	88
					
7[d]	**3k**	**13**	40	**15**	62

[a] Cyclotrimerizations were run with 5–6 equivalents of monoalkyne. [b] The isomer ratio was determined by NMR spectroscopy. [c] All reactions were carried out in toluene. Yields refer to products obtained after column chromatography. In general the respective isomers, in the case of **10**–**12** the main product, can be obtained in an isomerically pure form by repeated chromatography. [d] The reaction was carried out in CH_2Cl_2.

21.49 (q); elemental analysis (%) for $C_{17}H_{19}NO_3S$ (317.40): calcd.: C 64.33, H 6.03, N 4.41; found.: C 63.90, H 5.95, N 4.39.

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Keywords: alkynes · cyclotrimerizations · homogeneous catalysis · indolines · rhodium

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[13] 2,3-Dihydropyrroles originating from a 1,5-C-H insertion of alkylidene carbenes formed in situ were not observed.[9] For additions of nitrogen nucleophiles to alkynyliodonium salts and formation of 2,3-dihydropyrroles see: a) K. S. Feldman, M. M. Bruendl, K. Schildknegt, A. C. Bohnstedt, *J. Org. Chem.* **1996**, *61*, 5440–5452; b) K. Schildknegt, A. C. Bohnstedt, K. S. Feldman, A. Sambandam, *J. Am. Chem. Soc.* **1995**, *117*, 7544–7545.

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[14] All new compounds were characterized by ^{1}H, ^{13}C NMR, IR spectroscopy, mass spectrometry, C,H,N analysis, and/or high-resolution mass spectrometry.
[15] Grigg et al. suggested that polar solvents favor ligand dissociation and thereby accelerate the catalysis.[10g] However, in the examples studied by us, cyclotrimerizations occurred in toluene, which may be due to an enhanced reactivity of the *N*-1-alkynylamides for cyclotrimerizations in comparison with that of the diynes studied by Grigg.
[16] Additional monosubstituted alkynes, such as phenyl acetylene and 1-pentyne, undergo cyclotrimerization reactions with the diynes **4a**, **3i**, and **3j**. Further studies are in progress to explore the mechanistic factors responsible for the selectivity, as well as cyclotrimerization studies with nickel and cobalt catalysts.
[17] The structural assignment of compound **12a** is based on 2D-NMR experiments (H, H- and C, H-COSY, as well as HMBC) and distinct NOE relationships. We would like to thank Prof. Dr. L Ernst (Technische Universität Braunschweig) for the NOE measurements.

Tricyclopropylamine and Its Radical Cation**

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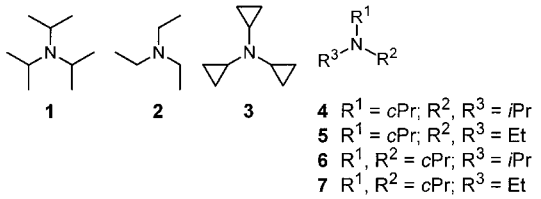
Dedicated to Professor George Olah on the occasion of his 70th birthday

In view of the report by Bock et al.[1] that triisopropylamine (**1**) is nearly planar at the nitrogen atom, and can, therefore, be oxidized unusually easily to a persistent radical cation, tricyclopropylamine (**3**) appeared to be a particularly interesting target for synthesis. In terms of the steric demand, a cyclopropyl group is significantly smaller than an isopropyl group[2] and slightly larger than an ethyl substituent, but is a far better electron donor to adjacent electron-deficient centers than any other alkyl group.[2, 3] Thus the three cyclopropyl groups in **3** should stabilize its radical cation $\mathbf{3}^{\bullet+}$ exceptionally well, so that the latter might be formed even more readily than the radical cations of **1** and triethylamine (**2**), just as the tricyclopropylmethyl cation emerges as a particularly stable tertiary carbenium ion.[4] Since neither S_N1 nor S_N2 displacements on cyclopropyl derivatives are easily achieved, **3** could not be prepared by straightforward cyclopropylation of cyclopropylamine. Fortunately, however, we were able to develop a new general synthesis of cyclopropyldialkylamines from acid dialkylamides[5, 6] which was readily adapted for the preparation of **3**.[7]



X-ray crystal structure analyses of tricyclopropylamine **3** at 130 K (Figure 1 A)[9] and its hydrochloride at 200 K[11] revealed that both have about the same pyramidal arrangement at the nitrogen atom ($\Sigma(\sphericalangle$C-N-C$) = 330.3^\circ$). Moreover, the orientation of all three cyclopropyl groups with respect to the lone pair on the nitrogen atom in **3** and to the N–H axis in **3**·HCl is exactly the same as that determined by computational[12, 13] and microwave-spectroscopic[13] studies on gas-phase cyclopropylamine. A gas-phase electron diffraction (GED) structure analysis of **3** established that the molecule in the free state has essentially the same conformation (Figure 1 B)[14] as in the crystal.

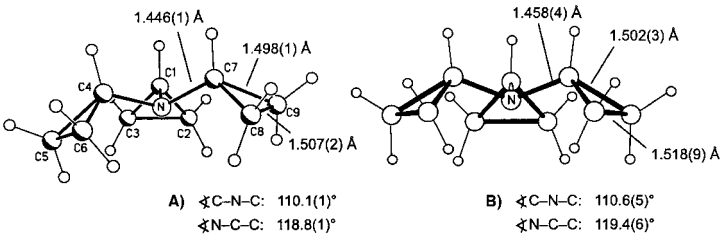


Figure 1. Structures of **3** in the crystal at 130 K (A)[9] and in the gas phase (B).[14] The distances and angles given for crystalline **3** are mean values; the interplanar angles between the plane C1,C4,C7 to the planes N,C1 and center of C2–C3; N,C4 and center C5–C6; N,C7 and center C8–C9 are 97.5, 83.9, and 93.8°, respectively. Shortest H···H distance 2.380(58) Å.

In this conformation, electron density can be delocalized from the nitrogen lone pair into the symmetric components of the cyclopropyl LUMOs.[12] In accord with the greater bulk of the isopropyl compared to the cyclopropyl groups, the C–N bonds in **3** (1.446(1) Å) are shorter than those in **1** (GED: 1.460(5) Å[3], X-ray structure analysis at 84 K: 1.469(1) Å[15]),

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