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A Ruthenium Complex-Catalyzed Cyclotrimerization of Halodiynes with Nitriles. Synthesis of 2- and 3-Halopyridines

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Abstract: Monohalo- and dihalodiynes efficiently undergo [2+2+2]cyclotrimerization with nitriles in the presence of a catalytic amount of the ruthenium complex Cp*RuCl(cod) (10 mol%) to afford the corresponding halopyridines under ambient conditions in good isolated yields (up to 90%). The halopyridines are formed as two separable regioisomers. This is the first example of a direct synthesis of halopyridines from haloalkynes and nitriles.

Keywords: alkynes; cyclotrimerization; homogeneous catalysis; nitrogen heterocycles; ruthenium

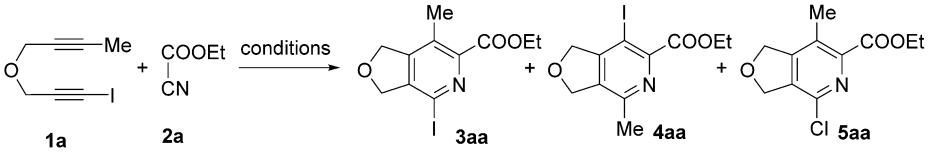
Pyridines and their more complex derivatives are an important class of heteroaromatic compounds. Substances possessing the pyridine framework are found in numerous branches of chemistry.[1] Out of many synthetic methods used for their preparation,[2] perhaps the simplest and the most efficient, is catalytic cyclotrimerization of alkynes with nitriles by using transition metal compounds.[3]

Although a number of catalytic protocols have been developed, there is still a considerable space to explore cyclotrimerization for hitherto untried combinations of alkynes and nitriles. In this respect, it would be desirable to develop a procedure allowing synthesis of pyridines possessing a reactive functional group on the pyridine scaffold that would allow further transformations. It would be synthetically interesting if a cyclotrimerization would allow formation of halopyridines by a catalytic reaction of haloalkynes with nitriles.

As far as the cyclotrimerization of chloro-, bromo- and iodoalkynes is concerned, they can efficiently react with alkynes in cyclotrimerization processes to give the corresponding halobenzenes. These processes include: (i) Ru- or Co-catalyzed reactions of monoiododiynes and diiododiynes[4] with alkynes to iodobenzenes that were further functionalized by cross-coupling reactions;[5] (ii) Ru- or Rh-catalyzed cyclotrimerization of monobromodiynes with alkynes as a route to new potentially selective inhibitors of tyrosine kinase 2;[6] (iii) Ru-catalyzed cyclotrimerization of a highly substituted chlorodiyne and alkyne during the course of the sporolide B synthesis.[7] Although, a Ru-complex catalyzed cycloaddition of haloalkynes with nitrile oxides and organic azides has been recently described,[8] their cyclotrimerization with nitriles providing halopyridines, interestingly, has not been reported so far (to the best of our knowledge). Our interest in cyclotrimerization of the halodiynes with the nitriles stemmed for the fact that this procedure could be used as an important step in syntheses of pyridines and derivatives thereof. They can be used in numerous homogeneous catalytic racemic or enantioselective processes as ancillary ligands and their derivatives (e.g., *N*-oxides, etc.) as Lewis basic organocatalysts.[1b,c,9] One such an example is Bolm's ligand, which has the bipyridine scaffold.[10] Therefore, it would be thus desirable to develop the cyclotrimerization of halodiynes with alkynes to substituted halopyridines, because they could serve as convenient intermediates for synthesis of bipyridines and other types of pyridine based ligands.

At the outset, the cyclotrimerization of iododiyne **1a** with ethyl cyanoformate **2a** as model compounds was screened under different conditions, to explore a possibility for the preparation of iodopyridines (Table 1). The reaction was carried out in dichloroethane (DCE) in the presence of a large excess of cyanoformate (20 equiv.) to ensure high conversion by using the previously reported conditions for Ru-catalyzed cyclotrimerization of iodoalkynes with alkynes

Table 1. Catalytic cyclotrimerization of **1a** with **2a** under different conditions.



Entry	**2a** (equiv.)	Catalyst[a]	(mol%)	Time [h]	Solvent[b]	Yield [%][c]			
						3aa	**4aa**	**5aa**	Combined
1	20	Ru	6	88	DCE	23	33	3	59
2	1	Ru	5	27	DCE	18[d]	19[d]	3[d]	40[d]
3	2	Ru	5	27	DCE	32[d]	39[d]	5[d]	76[d]
4	5	Ru	5	27	DCE	26[d]	28[d]	2[d]	56[d]
5	10	Ru	5	27	DCE	16[d]	21[d]	2[d]	39[d]
6	2	Ru	2	136	DCE	9	7	1	17
7	2	Ru	5	136	DCE	19	28	3	50
8	2	Ru	10	37	DCE	29	45	5	79
9	2	Ru	10	39	DCM	27	38	5	70
10	2	Ru	10	39	THF	27	45	5	77
11	2	Ru	10	39	$CHCl_3$	35	47	7	89
12	2	Ru	10	39	CPME	34	49	5	88
13	5	Co[e]	5	82	toluene	nr	nr	–	–
14	2	Rh[f]	2.5	36	DCE	traces	traces	–	–

[a] Ru = Cp*RuCl(cod); Co = CpCo[P(OEt)$_3$]diethylfumarate; Rh = [Rh(cod)]BF_4, (*R*)-BINAP. Reactions were run at 20 °C unless otherwise noted.
[b] DCE = 1,2-dichloroethane, DCM = dichloromethane, CPME = cyclopentyl methyl ether.
[c] Isolated yields unless otherwise noted; nr = no reaction.
[d] Yields determined by ^{1}H NMR.
[e] The reaction was run at 100 °C.
[f] The reaction was run at 20 °C (20 h) and then at 50 °C (16 h).

[Cp*RuCl(cod) at 20 °C]. Gratifyingly, the cyclotrimerization took place and provided three products **3aa**, **4aa**, and **5aa** in 23, 33, and 3% isolated yields (59% combined yield) (entry 1). Compounds **3aa** and **4aa** were regioisomers formed by different insertion pathways into the intermediate ruthenacycle, whereas **5aa** possessed chlorine instead of iodine. The formation of this compound was a bit puzzling, but subsequent investigation could reveal the origin of its formation (*vide infra*). Then, the effects of the nitrile/alkyne ratio, catalyst load and solvent on the course of the reaction were explored. The obtained results (entries 2–5) indicated the 2/1 nitrile/diyne ratio to be optimal giving products in 76% combined yield. Using 10 mol% of the catalyst seemed to be optimal for high yields of the products (entries 6–8). As far as the reaction medium is concerned, cyclotrimerization proceeded to give high isolated yields of the products (77–89%) in dichloromethane, tetrahydrofuran, chloroform, and cyclopentyl methyl ether (entries 9–12). Attempts to induce the cyclotrimerization with Co or Rh catalysts were not successful, despite the fact that these catalysts were shown to catalyze the cyclotrimerization of iodoalkynes with alkynes.[4e,5] In both cases the reaction did not take place; moreover, slight decomposition of iodoalkyne **1a** was observed (entries 13 and 14). Although speculative, their inactivity may arise from a competitive oxidative addition of the reactive *sp*C–halogen bond that might oxidatively add to these compounds providing catalytically inactive species.[11] With respect to the above described results, the following conclusions could be made on the optimal reaction conditions: (i) 2/1 nitrile/alkyne ratio, (ii) 10 mol% of Cp*RuCl(cod), (iii) chlorinated solvents as the reaction medium, (iv) reaction temperature of 20 °C. The structure of the regioisomers was unequivocally confirmed by single crystal X-ray analyses of **3aa** and **4aa** (Figure 1 and Figure 2).

Then the efficacy of the Ru-catalyzed cyclotrimerization of bromo- **1b** and chlorodiynes **1c** with cyanoacetate **2a** was examined for comparison under the optimized conditions (Table 2). The reaction with bromodiyne **1b** proceeded with full conversion of the starting material and provided a mixture of **3ba**, **4ba**, and **5aa** in a combined 91% isolated yield (entry 2). The use of the chlorodiyne **1c** furnished **3ca** and **4ca** in a lower yield of 72% (entry 3). Obviously, the use of the bromo derivative **1b** was advantageous with respect to yields of products. Attempts to increase the reaction rate of cyclotrimerization of **1b** by using AgOTf to generate a cationic complex[12] or to sup-

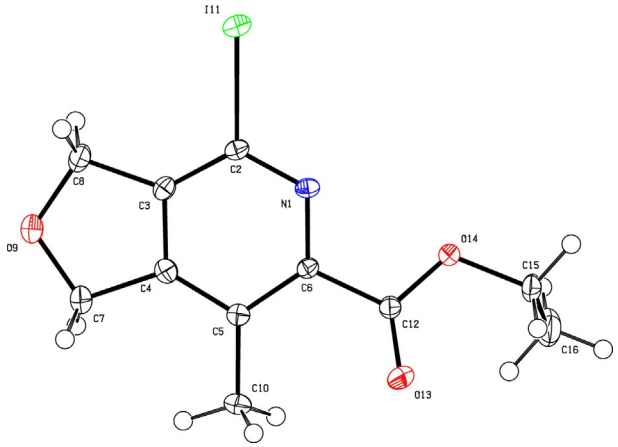


Figure 1. ORTEP drawing of **3aa** with 30% thermal ellipsoids.

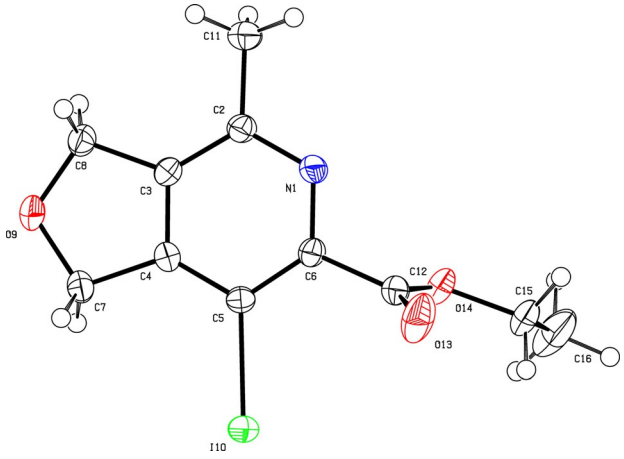


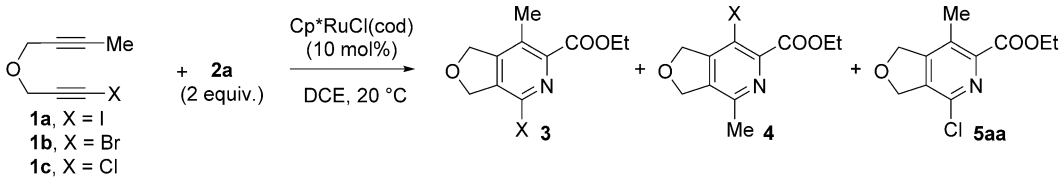
Figure 2. ORTEP drawing of **4aa** with 30% thermal ellipsoids.

press formation of **5aa** by addition of Bu_4NBr did not meet with success. The former resulted in the formation of a complex reaction mixture, in which only traces of the desired products were detected (entry 4). The latter had only a marginal if any effect on the product distribution (entry 5).

In order to elucidate the formation of the chloro derivatives, the following experiments were carried out, Firstly, **3aa** (containing approximately 12% of **5aa**) was mixed with an equimolar amount of Cp*RuCl(cod) in deuterated dichloromethane and stirred at 20 °C. According to the ^{1}H NMR analysis of the reaction mixture (thanks to characteristic signals of **3aa** and **5aa**) already 50% of **3aa** was converted to **5aa** after 10 h while after 10 days the conversion was 80% (see Figure SI-1 and Figure SI-2 in the Supporting Information).

A halogen exchange reaction is a synthetically interesting reaction proceeding in the presence of various transition metal compounds, including ruthenium complexes.[13] The Ru-catalyzed halogen exchange has been observed with triflates ([Cp*Ru(MeCN)$_3$]OTf and LiBr)[14] and acyl halides (CpRuCl(PPh$_3$)$_2$ with Me(CO)X, X = Cl, Br, I).[15] As for the reaction mechanism of the Ru-catalyzed halide exchange, two hypotheses have been proposed. The first one assumes the halogen exchange to proceed *via* oxidative addition forming a cationic Ru(IV) 18 electron complex followed by ligand exchange (TfO^- for X^-) and subsequently undergoing reductive elimination. The second one, based on experimental results and DFT calculations, proposes the course of the reaction to proceed *via* a radical pathway. Since thermochemical data clearly show that in 2-chloropyridine the C–Cl bond [BDE (C–Cl) = 90.5 kcal mol^{-1}][16] is much stronger than the C–I bond in 2-iodopyridine [BDE (C–I) = 63.1 kcal mol^{-1}].[17] We assume this difference in

Table 2. Ru-catalyzed cyclotrimerization of diynes **1** with nitrile **2a**.



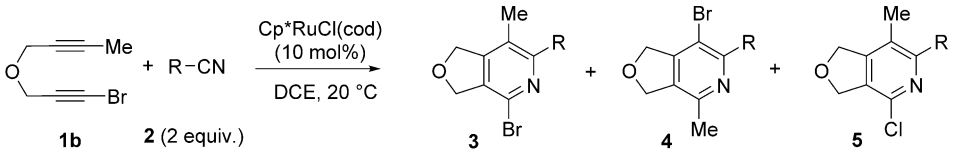
Entry	**1** (equiv.)	Time [h]	Additives	Yield [%][a] **3**		**4**		**5aa**[b]	Combined
1	**1a**	37	–	**3aa**	29	**4aa**	45	5	79
2	**1b**	21	–	**3ba**	40	**4ba**	48	3	91
3	**1c**	21	–	**3ca**	36	**4ca**	36	–[b]	72
4	**1b**	39	AgOTf	**3ba**	traces	**4ba**	traces	traces	–
5	**1b**	20	Bu_4NBr	**3ba**	31	**4ba**	39	2	72

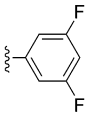
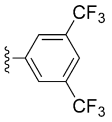
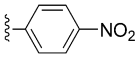
[a] Isolated yields.
[b] The compound's structure is the same as that of **3ca.**

bond strength to be the driving force of the reaction.[18] To verify this assumption 2-iodopyridine was stirred with Cp*RuCl(cod) in deuterated dichloromethane. The exchange proceeded in the same fashion, but the reaction rate was much faster: 50% conversion to 2-chloropyridine was observed already after 5 hours and 90% conversion after 48 h (see Figure SI-3 and Figure SI-4 in the Supporting Information). However, attempts to carry out the iodine-chlorine exchange under catalytic conditions [10 mol% Cp*RuCl(cod)] in the presence of LiCl (THF, MeOH, DMF) or Me_4NCl (DCE/MeOH) in various solvents were not met with success and only traces (~1–2%) of the desired 2-chloropyridine were observed after prolonged reaction time (1 week) even if the temperature was increased to 50 °C.

Having elucidated the formation of the chloro derivatives, we decided to proceed with an assessment of the reaction scope and the cyclotrimerization of various nitriles **2** with **1b** was undertaken (Table 3). Although the reaction with cyanoformate **2a** proceeded to give high yields of products (Table 2, entry 2), the reactions with other nitriles gave variable yields. Thus the reaction with cyanoacetate **2b** at 20 or 50 °C did not yield the desired products. On the other hand, the use of highly electron-deficient malononitrile **2c** at 20 °C provided a mixture of **3bc** (59%) and **4bc** (13%) yield along with minor amount of **5ac** (2%) (entry 1). A possible product of the double cyclotrimerization was not observed. A reaction of **1b** with benzonitrile **2d** and 4-chlorobenzonitrile **2e** did not provide the expected products at 20 or 50 °C. Interestingly, reaction with 3,5-difluorobenzonitrile **2f** and 2,4,6-trifluorobenzonitrile **2g** gave opposite results. The former gave rise to **3bf** and **5af** in 16% and 3% isolated yields, respectively (entry 2), whereas **4bf** was formed just in traces (~1%). Gratifyingly, the use of highly electron-deficient nitrile **2h** at 20 or 50 °C pro-

Table 3. Ru-catalyzed cyclotrimerization of various nitriles **2** with **1b**.



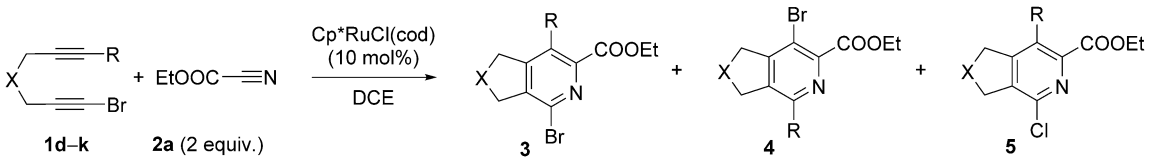
Entry	2	R =	Temp. [°C]	Time [h]	Yield [%][a] 3		4		5		Combined
1	**2c**		20	13	**3bc**	59	**4bc**	13	**5ac**	2	74
2	**2f**		20	143	**3bf**	16	**4bf**	traces	**5af**	3	19
3	**2h**		20	40	**3bh**	30	**4bh**	nd[b]	**5ah**	5	35
4	**2i**		20	69	**3bi**	31	**4bi**	12	**5ai**	5	48
5	**2j**		50	10	**3bj**	31	**4bj**	8	**5aj**	5	44[c]
6	**2l**		20	11	**3bl**	48	**4bl**	33	**5al**	1	82
7	**2m**		20	15	**3bm**	32	**4bm**	11	**5am**	2	45
8	**2n**		20	12	**3bn**	51	**4bn**	13	**5an**	3	67

[a] Isolated yields.
[b] nd = not detected.
[c] An inseparable mixture of regioisomers. The ratio was determined from ^{1}H NMR.

vided **3bh** in 30% yield, along with a minor amount of **5ah** (5%) (entry 3). Interestingly, formation of regioisomer **4bh** was not detected. The use of electron-deficient nitriles such as 3,5-bis(trifluoromethyl)benzonitrile **2i** and 4-nitrobenzonitrile **2j** resulted in the formation of both regiosiomers. The former furnished **3bi** and **4bi** in 31% and 12% isolated yields along with **5ai** (5%) (entry 4). The latter furnished **3bj** and **4bj** in 27% and 5% isolated yields along with **5aj** (6%). Carrying out the reaction at 50 °C had only marginal effect on the overall yields of products and provided **3bj**, **4bj**, and **5aj** in 31, 8, and 5% yields, respectively (entry 5). Interestingly, the reaction with 1,4-dicyanobenzene **2k** gave rise only to traces of the expected products. Then our attention turned to acyl cyanides such as acetyl cyanide **2l**, pivaloyl cyanide **2m** and benzoyl cyanide **2n**. In all cases the reaction proceeded at 20 °C to give mixtures of both regioisomers in good isolated yields (entries 6, 7, and 8). Formation of chloro derivatives **5al–5an** was observed in the usual extent (1–3%). The above mentioned results indicate that only strongly electron-deficient nitriles enter this type of cyclotrimerization reaction. It should be also noted that somewhat better results, that is, up to 15% higher yields, were obtained with new batches of the catalyst, indicating that the course of the reaction with respect to conversions and yields could be affected by the catalyst quality.

The scope of the reaction with respect to diynes was tested afterwards (Table 4). Cyclotrimerizations were carried out with 1-bromo- **1d**, 1-bromo-1′-phenyl- **1e**, and 1-bromo-1′-trimethylsilyl- **1f** dipropargyl ethers giving rise to the corresponding mixtures of regioisomers **3da–3fa** and **4da–4fa** in good combined yields of 36, 55, and 87% (entries 1–3). It is worth noting that the reaction with **1d** provided only regioisomer **3da**, the other one – **4da** – was not detected in the reaction mixture and the reaction had to be carried at 50 °C. Interestingly, a reaction with 1-bromo-1′-cyclopropyl dipropargyl ether **1g** did not proceed at 20 or at 50 °C (entry 4). The discrepancy in reactivity of **1f** and **1g** cannot be simply rationalized in terms of steric hindrance, because according to the Charton parameters,[19] the trimethylsilyl group (ν = 1.40) should exert larger steric hindrance than the cyclopropyl group (ν = 1.06). In addition, a complex reaction mixture was obtained in the reaction with **1g** and, according to its ^{1}H NMR analysis, the presence of other compounds possessing the cyclopropane ring was not noticed. Hence side-reactions involving cleavage of the cyclopropane ring might hamper the overall outcome of the cyclotrimerization. The use 1-bromo-1,6-heptadiyne **1h** did not provide the expected pyridine derivatives **3ha** and **4ha** (entry 5); preferential homocyclotrimerization to a bromobenzene **SI-1** was observed instead. A similar result was observed in cyclotrimerization of diethyl 2-(3-bromoprop-2-ynyl)-2-(prop-2-ynyl)malonate **1i** in which homocyclotrimerization to **SI-2** was the major reaction pathway. In spite of that, **3ia** was isolated in low yield of 12% and only traces of **4ia** were detected (entry 6). On the other hand, cyclotrimerization of diethyl 2-(3-bromoprop-2-ynyl)-2-(but-2-ynyl)malonate **1j** with **2a** proceeded to give **3ja** and **4ja** in 31 and 38% yields, respectively (entry 7). Cyclotrimerizations of 1-bromo-1,7-octadiyne **1k** with **2a** did not give the desired products (entry 8). These results are not so much surprising since a similar phenomenon had been ob-

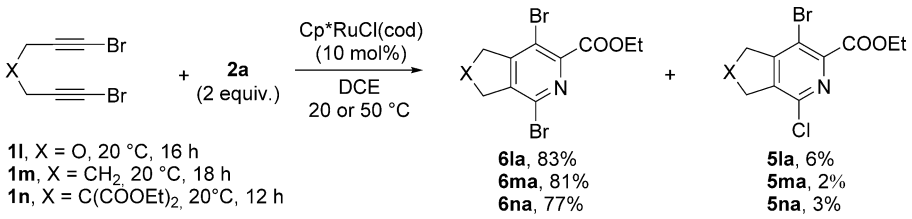
Table 4. Ru-catalyzed cyclotrimerization of various diynes **1** with **2a**.



1d–k **2a** (2 equiv.) **3** **4** **5**

Entry	1	X	R =	Temp. [°C]	Time [h]	Yield [%][a] 3		4		5		Combined
1	**1d**	O	H	50	24	**3da**	32	**4da**	nd[b]	**5da**	4	36
2	**1e**	O	Ph	20	22	**3ea**	32	**4ea**	17	**5ea**	6	55
3	**1f**	O	TMS	20	13	**3fa**	44	**4fa**	36	**5fa**	7	87[c]
4	**1g**	O	*c*-Pr	50	47	**3ga**	traces	**4ga**	traces	**5ga**	traces	–
5	**1h**	CH_2	H	20	66	**3ha**	nr[b]	**4ha**	nr[b]	**5ha**	–	–[d]
6	**1i**	$C(COOEt)_2$	H	20	82	**3ia**	12	**4ia**	traces	**5ia**	2	14[d]
7	**1j**	$C(COOEt)_2$	Me	20	18	**3ja**	31	**4ja**	38	**5ja**	2	71
8	**1k**	$(CH_2)_2$	H	50	24	**3ka**	traces	**4ka**	traces	**5ka**	–	–[d]

[a] Isolated yields.
[b] nd = not detected, nr = no reaction.
[c] An inseparable mixture of regioisomers. The ratio was determined from ^{1}H NMR.
[d] Homocyclotrimerization of the starting diyne was observed.

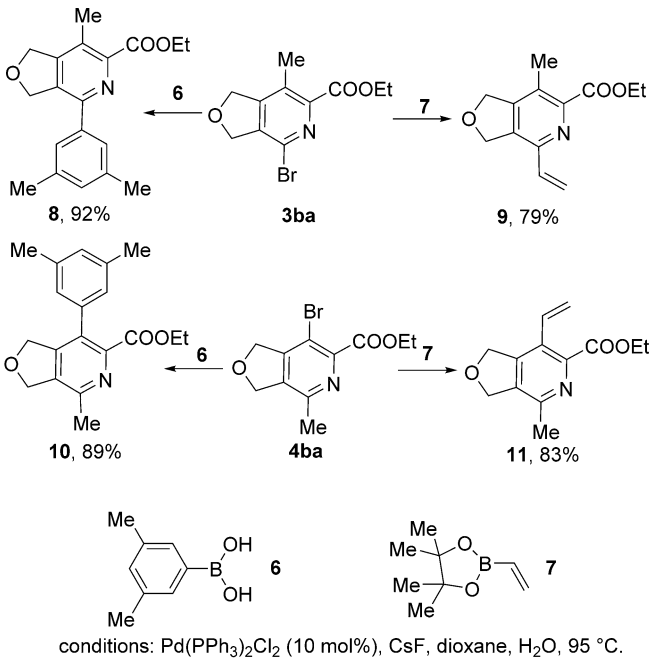


Scheme 1. Cyclotrimerizations of dibromodiynes **1l–1n** with **2a**.

served in Ru-[4e] as well as in Rh-catalyzed[20] cyclotrimerizations of halodiynes previously. It should be noted that in cases of cyclotrimerization of diynes possessing the terminal triple bond (**1h**, **1i**, and **1k**) homocyclotrimerization of diynes was observed as an undesirable side reaction (in case of **1k** only traces of the benzene product were detected by ^{1}H NMR analysis of the reaction mixture).

Finally cyclotrimerization of **2a** with 1,1′-dibromodiynes was screened (Scheme 1). In the case of dibromodiynes **1l–1n** cyclotrimerization proceeded uneventfully and furnished the desired products **6la–6na** in high isolated yields of 83, 81, and 77%, respectively. In all cases also chloro derivatives **5la–5na** were formed as minor by-products (2–6%). As expected on the base of previous results (entry 8, Table 4) cyclotrimerization of 1,8-dibromo-1,7-octadiyne **1o** did not give the desired product either at 20 or at 50 °C.

Last but not least, utilization of the prepared bromopyridines **3ba** and **4ba** in cross-coupling reactions



Scheme 2. Cross-coupling of **3ba** and **4ba** with boronic acid derivatives **6** and **7** under Suzuki conditions.

with 3,5-dimethylphenylboronic acid **6** and vinylboronic acid pinacol ester **7** was briefly screened (Scheme 2). Thus reaction of **3ba** with **6** and **7** under the recently reported Suzuki coupling conditions[21] [$Pd(PPh_3)_2Cl_2$ (10 mol%), CsF, dioxane, H_2O, 95 °C] provided the expected phenylated and vinylated products **8** and **9** in very good 92 and 79% isolated yields, respectively. Analogously proceeded the reactions with **4ba** that gave rise to phenylated and vinylated products **10** and **11** in nice 89 and 83% isolated yields, respectively.

In summary, (i) 1-halo- and 1,7-dibromoheptadiynes could be successfully cyclotrimerized with electron-deficient nitriles to the corresponding halopyridines under catalysis of the Ru-complex (10 mol% of the catalyst is required); (ii) the optimal nitrile/alkyne ratio is 2/1; (iii) the optimal reaction temperature is 20 °C, in the case of less reactive alkynes/nitriles, 50 °C could be used, (iv) the reaction can be run in different solvents such as chloroalkanes or ethers, (v) for the reactions of **1a**, **1b**, and **1j** with **2a** a slight preference for 3-halopyridine is observed, whereas for other cases a slight preference for the formation of 2-halopyridines was observed. A brief study regarding cross-coupling reactions of the regioisomeric products was undertaken: both regioisomers reacted almost quantitatively providing basic proof of concept for further functionalization.

Experimental Section

Ethyl 4-Iodo-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (3aa), Ethyl 7-Iodo-4-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (4aa), and Ethyl 4-Chloro-7-methyl-1,3-dihydrofuro[3,4-*c*]pyridine-6-carboxylate (5aa)

Into a dried flask containing Cp*RuCl(cod) (7.6 mg, 0.02 mmol) under an argon atmosphere, DCE (1 mL) and nitrile **2a** (40 mg, 0.4 mmol) were slowly added. Then diyne **1a** (47 mg, 0.2 mmol) dissolved in DCE (1.2 mL) was added during the course of 15 min and the reaction mixture was stirred at 20 °C. After the full consumption of the starting diyne (disappearance of the respective spot from TLC analysis), volatiles were evaporated under reduced pressure. Column chromatography of the residue on silica gel (gradi-

ent 10/1→5/1 hexanes/EtOAc) furnished 22 mg of an inseparable mixture of **3aa** and **5aa** (yields: 29% and 5% determined from ^{1}H NMR) and 30 mg (yield: 45%) of **4aa** as colourless solids. The combined yield is 79%.

3aa: mp 168 °C (for a mixture containing **5aa**); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.24$ (t, $J = 2.4$ Hz, 2H, CH_2), 5.05 (t, $J = 2.4$ Hz, 2H, CH_2), 4.44 (q, $J = 7.1$ Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.42 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 165.23$, 150.24, 148.83, 143.74, 128.30, 106.17, 76.44, 74.52, 62.18, 15.76, 14.37; IR (**3aa**+**5aa**; drift KBr): $\nu_{max} = 2977$, 1709, 1467, 1413, 1380, 1281, 1183, 1063, 1099, 905 cm^{-1}; HR-MS (EI-TOF): $m/z = 332.9861$, calculated for $C_{11}H_{12}NO_3I$ (M): 332.9862; R_f (5/1 hexanes/EtOAc) = 0.31 (the same value for **3aa** and **5aa**).

3ca: mp 112.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.18$ (s, 4H, 2×CH_2), 4.44 (q, $J = 7.1$ Hz, 2H, CH_2), 2.41 (s, 3H, CH_3), 1.42 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 165.21$, 153.15, 147.58, 141.41, 136.33, 128.08, 74.08, 73.18, 62.20, 15.88, 14.38; IR (drift KBr): $\nu_{max} = 1715$, 1470, 1416, 1311, 1290, 1260, 1186, 1066, 1039, 905 cm^{-1}; HR-MS (EI-TOF): $m/z = 241.0503$, calculated for $C_{11}H_{12}NO_3Cl$ (M): 241.0506.

4aa: mp 113 °C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.26$ (t, $J = 2.1$ Hz, 2H, CH_2), 5.06 (t, $J = 2.1$ Hz, 2H, CH_2), 4.47 (q, $J = 7.1$ Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.44 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 166.17$, 155.36, 151.49, 151.02, 135.65, 80.69, 78.74, 73.78, 62.53, 21.70, 14.31; IR (drift KBr): $\nu_{max} = 1730$, 1419, 1377, 1335, 1308, 1204, 1159, 1060, 905, 854 cm^{-1}; HRMS (EI-TOF): $m/z = 332.9864$, calculated for $C_{11}H_{12}NO_3I$ (M): 332.9862; R_f (5/1 hexanes/EtOAc) = 0.16.

For further experimental details, characterization for all new compounds, and X-ray data,[22] see the Supporting Information.

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[22] CCDC 1442030 (**3aa**) and CCDC 1442031 (**4aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

