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[2+2+2]-Cyclotrimerization of 1-Cyclopropyl-1,6-diynes with Alkynes: Formation of Cyclopropylarenes.

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Abstract: Cyclotrimerization of 1-cyclopropyl-1,6-diynes with various terminal alkynes was tested under catalytic conditions using rhodium and ruthenium catalysts. We observed that the regioselectivity of the reaction, that is, formation of 1,2- or 1,3-regioisomers, was opposite for the two metals. For the ruthenium complex [Cp*Ru(cod)Cl]-catalyzed reactions the yields were in many cases high with a strong preference for the formation of 1,3-substituted regioisomers. In the case of catalysis by the rhodium complex $[RhCl(PPh_3)_3]$, 1,2-substituted products were generally preferred, albeit the selectivity was often modest. However, by changing the ligand environment around the central rhodium atom the regioselectivity as well as yields of the products were significantly improved. For example, by using a combination of the rhodium complex $[Rh(cod)_2BF_4]$ and 1,4-bis(diphenylphosphino)butane the regioselectivity was changed from 1:1 to 1:12 in favor of the 1,2-regioisomer. This catalytic system was also applied for synthesis of a substituted 4-cyclopropyl-3-hydroisobenzofuran-1-one that could serve as a potential intermediate for preparation of antihypertensive agents.

Keywords: arenes; cyclotrimerization; homogeneous catalysis; rhodium; ruthenium

Introduction

Cyclotrimerization of alkynes, thanks to their structural variability, constitutes one of the most efficient and straightforward synthetic techniques for the construction of variously substituted benzenes and other aromatic compounds. The cyclotrimerization can be promoted by either catalytic or stoichiometric amounts of transition metal compounds, each of these methodologies having its pros and cons, but they complement each other. This reaction has also been used in syntheses of valuable synthetic building blocks and has served as the key step in syntheses of numerous natural products.[1]

One such class of interesting building blocks are cyclopropylbenzenes (cyclopropylarenes) that have found applications in diverse fields of chemistry, thanks to the special electronic and steric properties exerted by the cyclopropyl group.[2,3] The cyclopropylarene moiety can be found in a number of compounds possessing various biological activities, such as enzyme inhibitory,[4] lipooxygenase inhibitory,[5] anti-HIV,[6] antihepatitis,[7] antiautoimmune,[8] antihypertensive (Figure 1)[9] or pesticidal effects.[10] The cyclopropylarenes have also served as starting materials for synthesis of chiral intermediates via enzymatic oxidation.[11] They are commonly prepared by cycloaddition of alkynes with dienes[12] or cross-coupling reactions using Suzuki[13] or other protocols.[14]

Interestingly, there has been just a handful of scattered reports regarding the formation of cyclopropylarenes via cyclotrimerization reaction. Among them belong Cp*Ru(cod)Cl and $\{[Ir(H)(rac\text{-BINAP})]_2(\mu\text{-}I)_3\}_3I$ catalyzed cyclotrimerization of diynes with cyclopropylethyne leading to cyclopropylated isoindolinones[15] and isoindolines[16] (1 example in each case), $Ni(cod)_2/PPh_3$ catalyzed homocyclotrimerization to a mixture of regioisomeric triscyclopropylbenzenes[17] and intramolecular cyclotrimerization of cyclopropylated triynes catalyzed by Ru-carbene complexes to the corresponding tricycles (3 examples).[18] Reports regarding cyclotrimerization of the structurally related *iso*-propylated alkynes have been scarce as well.[19]

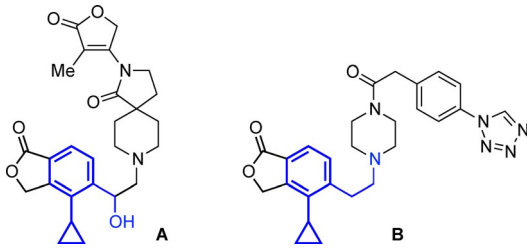


Figure 1. Compounds **A** and **B** tested in *in vivo* studies as renal outer medullary potassium channel (ROMK) inhibitors (potential antihypertensive agents).[9]

Because of our interest to explore the possibility of synthesizing cyclopropylated aromatic compounds by using the cyclotrimerization strategy, we undertook an effort to explore this approach and assess its scope and limitations with respect to transition metal based catalytic systems and the substrate structure. From the synthetic point of view, compounds **A** and **B** (Figure 1) attracted our attention, because they could, in principle, be accessed by cyclotrimerization of a suitably substituted cyclopropylated diyne with propargylic or homopropargylic alcohol or derivatives thereof.

Results and Discussion

The starting 1-cyclopropyl-1,6-diynes **1a-1c** (Figure 2) were prepared by using standard organic transformations from the commercially available cyclopropylethyne. It was treated with *n*-butyllithium followed by addition of paraformaldehyde to give 3-cyclopropylprop-2-yn-1-ol[20] in 83-90% yield. The alcohol was then reacted either with NaH and propargyl bromide to obtain diyne **1a** (in 79-89% yield) or with DCC and propiolic acid[21] to yield diyne **1b** (70%). For the synthesis of compound **1c** cyclopropylethyne was again deprotonated using *n*-butyllithium, this time treated with carbon dioxide in the form of dry ice, to give 3-cyclopropylpropiolic acid[22] in 92% yield. After the reaction with DCC and propargyl alcohol

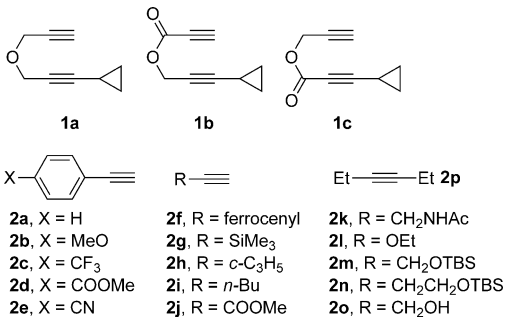


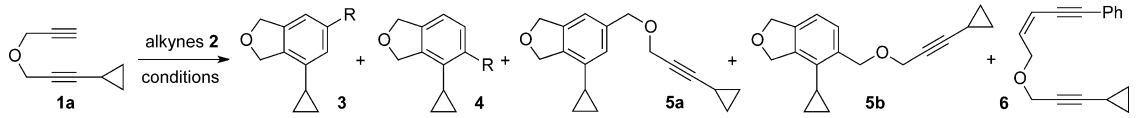
Figure 2. Diynes and alkynes used in the cyclotrimerization study.

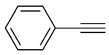
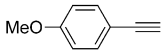
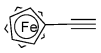
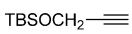
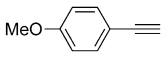
the desired ester **1c** was obtained (65%). All the alkynes tested in cyclotrimerization reaction are listed in Figure 2.

Initially, we screened the cyclotrimerization of **1a** with terminal alkynes **2a, 2b, 2f, 2h, 2i** and **2m** in the presence of a catalytic amount of $RhCl(PPh_3)_3$ (Wilkinson's catalyst) in toluene (Table 1). In almost all cases arenes **3** (4-cyclopropyl-1,3-dihydro-6-(substituted)-isobenzofurans, the 1,3-regioisomer) and **4** (4-cyclopropyl-1,3-dihydro-5-(substituted)-isobenzofurans, the 1,2-regioisomer) were formed, even though in rather low isolated yields (4-26% range) (Entries 1-10). In addition, the formation of regioisomeric homocyclotrimerization products **5a** and **5b**, which were in many cases the major products, along with (*Z*)-(5-(3-cyclopropylprop-2-ynyloxy)pent-3-en-1-ynyl)benzene **6** - the result of an alkyne addition to diyne **1a** - was observed. A slight preference for the formation 1,2-regioisomer **4** was observed in toluene (**3/4** ratio was in the range of 1/1-1.8). Interestingly, there were two exceptions from this rule: a) in the reaction with ferrocenylethyne **2f** the formation of 1,3-regioisomer **3f** was preferred (Entry 6); b) the reaction with the TBS-protected propargyl alcohol **2m** furnished 1.9/1 mixture of **3m** and **4m** (Entry 10). In addition, two cyclotrimerizations were performed in ethanol; but in both cases the yields were low and each led to preferential formation of a different regioisomer (Entries 4 and 8). Since it has been shown that the cationic Rh-complex prepared from $Rh(cod)_2BF_4$ and BINAP[1g,23] efficiently catalyzes cyclotrimerization of alkynes, it was applied in cyclotrimerization of **2h**. However, its use did not result in a better yield of the corresponding arenes **3h** and **4h** (18%) or regioselectivity (**3h/4h** = 1/1) (Entry 11). The cyclotrimerization of **2b** was also tested in the presence of the cobalt ($CpCo(CO)_2$) and nickel ($NiBr_2(PPh_3)_2$/Zn) catalytic systems. Nonetheless, the yields of the products **3b** and **4b** did not improve much, being 20 and 30%, respectively (Entries 12 and 13). Interestingly, regioselectivity differed significantly, the Co-catalyzed reaction provided **3b/4b** in 1/1 ratio, whereas the Ni-catalyzed reaction significantly favored formation of 1,3-regioisomer **3b** (**3b/4b** = 3.5/1). Our attempts to carry out cyclotrimerization with 3-hexyne **2p** (using $RhCl(PPh_3)_3$) did not provide any products and only homocyclotrimerization to **5** (81%, 1/1) was observed.

Then we tested Cp*Ru(cod)Cl as a catalyst to bring about cyclotrimerization (Table 2). Gratifyingly, its use led to higher conversions of the starting material furnishing the desired products **3** and **4** in better isolated yields (17-72%). The general preference for 1,3-substituted regioisomer was prevailing in all cases and was in the range of 6-15/1 (**3/4**). The reaction with phenylacetylene **2a** provided **3a** in a rather low yield of 20% in both dichloromethane or 1,2-dichloroethane (Entries 1 and 2). On the other hand, reaction

Table 1. Cyclotrimerization of **1a** with various alkynes **2** in the presence of Rh, Co, and Ni catalysts.



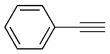
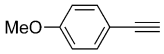
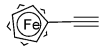
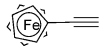
Entry	Alkyne **2**	**2** (equiv)	Cat[a]	Solvent[b]	t (h)	Products	Yield (%)[c]	**3/4**	**5**, Yield (%)[c,d]
1		**2a** (3)	A	toluene	24	**3a** + **4a**	25	1/1.4	63 (1/1)[e]
2		**2a** (5)	A	toluene	23	**3a** + **4a**	21	1/1.8	-- [f,g]
3		**2a** (10)	A	toluene	4	**3a** + **4a**	15	1/1.6	-- [g,h]
4		**2a** (3)	A	EtOH	43	**3a** + **4a**	10	1/1.3	21 (1.5/1)[i]
5		**2b** (3)	A	toluene	16	**3b** + **4b**	22	1/1.5	40 (1/1)
6		**2f** (2)	A	toluene	22	**3f** + **4f**	23	7/1	4 (1/1)
7		**2h** (2)	A	toluene	23	**3h** + **4h**	26	1/1	54 (1/1)
8		**2h** (3)	A	EtOH	43	**3h** + **4h**	4	1.7/1	6 (1.7/1)
9		**2i** (3)	A	toluene	20	**3i** + **4i**	4	1/1	-- [g,j])
10		**2m** (2)	A	toluene	68[k]	**3m** + **4m**	21	1.9/1	28 (2/1)[l]
11		**2h** (3)	B	DCE	24	**3h** + **4h**	18	1/1	22 (1/1)
12		**2b** (2)	C	THF	0.5[m]	**3b** + **4b**	20	1/1	-- [n]
13		**2b** (3)	D	MeCN	22	**3b** + **4b**	30	3.5/1	--

[a] Catalysts A = $RhCl(PPh_3)_3$ (5 mol%), B = $Rh(cod)_2BF_4$/BINAP (8 mol%), C = $CpCo(CO)_2$ (10 mol%), D = $NiBr_2(PPh_3)_2$/Zn (20 mol%).
[b] Reactions were carried out at 22 °C unless otherwise noted. DCE = CH_2ClCH_2Cl.
[c] Isolated yields.
[d] **5a**/**5b** ratio in brackets.
[e] **6** was isolated in 5% yield.
[f] **6** was isolated in 15% yield.
[g] **5** was formed but yield not determined.
[h] **6** was isolated in 25% yield.
[i] 21% of **1a** was recovered.
[j] 40% of **1a** was recovered.
[k] At 50 °C.
[l] 10% of **1a** was recovered.
[m] Microwave irradiation, 120 °C.
[n] 63% of **1a** was recovered.

with an electron rich 4-methoxyphenylacetylene **2b** gave the corresponding **3b** in a nice yield of 72% (Entry 3). The cyclotrimerization with bulky ferrocenylethyne **2f** gave rise to **3f** and **4f** in a good yield of 51% (Entry 4). The reaction with cyclopropylethyne **2h** and 1-hexyne **2i** furnished the corresponding products in 35 and 17% yield, respectively (Entries 5 and 6). Furthermore, the reaction with **2f** catalyzed by a Ru-carbene complex (Grubbs 1 st generation catalyst) was attempted, giving **3f** and **4f** in 31% yield (Entry 7).[24] Interestingly, the reactions with electron-poor alkynes such as (4-trifluoromethylphenyl)ethyne **2c** and (4-methoxycarbonylphenyl)ethyne **2d**, sterically hindered alkynes such as trimethylsilylethyne **2g**, or internal alkynes 3-hexyne **2p** and 1,4-butyndiol did not proceed, and only products of homocyclotrimerization **5** were observed in yields of 25% (6/1), 12% (8/1), 3%, 33% (10/1), and 78% (6/1), respectively. Attempts to add the diynes dropwise to the solution of the catalyst and excess monoalkynes did not have substantial effect on the product distribution.

Our attention then turned to ester **1b**, because its cyclotrimerization could provide products possessing structural features found in compounds **A** and **B** (Figure 1). A considerable improvement in yields of cyclotrimerizations of **1b**, in comparison with corresponding reactions of **1a**, with alkynes **2a-2n** was seen when Ru-catalysts were applied (Table 3). In

Table 2. Cyclotrimerization of **1a** with various alkynes **2** in the presence of Ru catalysts.[a]

Entry	Alkyne **2**	**2** (equiv)	Solvent[b]	t (h)	Products	Yield (%)[c]	**3/4**	**5**, Yield (%)[c,d]
1		**2a** (2)	DCM	23	**3a** + **4a**	20	8/1	15 (5/1)[e]
2		**2a** (2)	DCE	48	**3a** + **4a**	20	6/1	9 (5/1)
3		**2b** (3)	DCM	22	**3b** + **4b**	72	8/1	-
4		**2f** (2)	DCM	23	**3f** + **4f**	51	6/1	21 (6/1)
5		**2h** (2)	DCM	22	**3h** + **4h**	35	9/1	21 (7/1)[f]
6		**2i** (2)	DCM	26	**3i** + **4i**	17	15/1	12 (9/1)[g]
7[h]		**2f** (2)	DCM	23	**3f** + **4f**	31	4/1	--

[a] Cp*Ru(cod)Cl (10 mol%) was used unless otherwise mentioned.
[b] 22 °C, DCE = CH_2ClCH_2Cl, DCM = CH_2Cl_2.
[c] Isolated yields.
[d] **5a**/**5b** ratio in brackets.
[e] 36% of **1a** was recovered.
[f] 14% of **1a** was recovered.
[g] 37% of **1a** was recovered.
[h] Grubbs 1st generation catalyst was used.

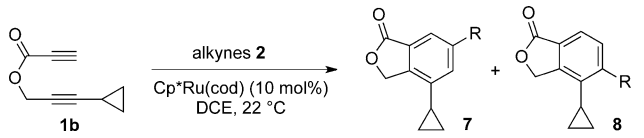
general, the corresponding 4-cyclopropyl-6-(substituted)isobenzofuran-1(3*H*)-ones **7** and 4-cyclopropyl-5-(substituted)isobenzofuran-1(3*H*)-ones **8** were formed and isolated in high yields with a significant preference for the 1,3-substituted products (**7/8** ratio was in the range of 2.5-8/1). Homocyclotrimerization of **1b** was not observed. Only the reactions with trimethylsilylethyne **2g** and methyl propynoate **2j** gave mediocre isolated yields of the corresponding products: 49 and 28% (Entries 7 and 11). In addition, the reaction with **2f** catalyzed by Grubbs 1st generation catalyst was conducted and furnished **7f** and **8f** in 46% yield but no regioselectivity (Entry 16). The reaction of **1b** with 3-hexyne **2p** provided the corresponding product in a very low yield of 9%. The attempts to utilize Rh-catalysis ($RhCl(PPh_3)_3$) for cyclotrimerization of **1b** with cyclopropylethyne **2h**, 1-hexyne **2i**, and 3-hexyne **2p** furnished products in very low if any yields: 4 (1/1), 7 (1/1) and 0%, respectively, along with the formation of homocyclotrimerization products of **1b** (**9**) and unreacted starting material.

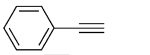
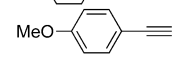
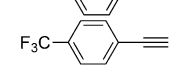
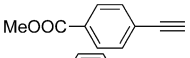
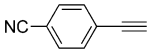
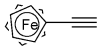
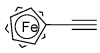
Although the regioisomeric products **3/4** and **7/8** were generally inseparable by means of chromatographic methods, the recrystallization of the products **7f** and **8f** obtained from the reaction of **1b** with ferrocenylethyne **2f** gave a mixture of differently shaped yellow and red crystals that were separated manually. The subsequent X-ray structure analysis enabled us to unequivocally determine the structure of **7f** (yellow crystals) and **8f** (red crystals) (Figure 3). We were also able to obtain crystals of **7d** suitable for X-ray analysis (see the SI).

Since the above mentioned reactions catalyzed by the Ru-complex were carried out with a rather high catalyst loading of 10 mol% (this amount was used because of a relatively small reaction scale using 0.25 mmol of **1b**), additional experiments aiming to reduce the loading and to evaluate solvent effects were carried out. Cyclotrimerization of **1b** with cyclopropylethyne **2h** was chosen as a model reaction. The results summarized in Table 4 clearly show that the reaction proceeded with excellent yields in DCE even in the presence of 2 mol% of the catalyst at 22 °C (Entry 4). As far as the solvents are concerned, the cyclotrimerization was also carried out in THF and cyclopentyl methyl ether (CPME), both used as the solvent of choice in previous reports (Entries 6-8).[15,23c] In both instances the yields were very high. It is worth mentioning that in CPME the **7h**/**8h** ratio was slightly increased to 8/1 in comparison with other cases (Entry 8). The reaction proceeded well even in chloroform (Entry 9). These results indicate that not only chlorinated solvents, but also ether-based solvents could be optimal media to carry out Ru-catalyzed cyclotrimerization.

As for the regioselectivity of the Ru-catalyzed cyclotrimerization, the preferential formation of 1,3-regioisomer in the Ru-catalyzed reactions is in line with the previously reported data and could be reasonably explained by steric factors during the insertion of an alkyne to the formed ruthenium intermediate.[25] The better regioselectivity in case of products **3/4** in comparison to products **7/8** can be attributed to the electron deficient nature of the terminal triple bond in the substrate **1b** which observation is in a good accord with the results of Yamamoto.[25c] Diyne **1b** is also less prone to homocyclotrimerization than **1a** for the same reason.

Table 3. Cyclotrimerization of **1b** with various alkynes **2** in the presence of Ru-catalysts.



Entry	Alkyne 2[a]		t (h)	Products	Yield (%)[b]	7/8
1		**2a**	6	**7a + 8a**	83	3/1
2		**2b**	6	**7b + 8b**	87	3/1
3		**2c**	4	**7c + 8c**	85	4/1
4		**2d**	24	**7d + 8d**	75	3.7/1
5		**2e**	4	**7e + 8e**	85	3/1
6		**2f**	4	**7f + 8f**	89	2.6/1
7	Me_3Si—	**2g**	5	**7g + 8g**	49	8/1
8		**2h**	22	**7h + 8h**	84	5.7/1
9[c]		**2h**	21	**7h + 8h**	84	6/1
10	*n*-Bu—	**2i**	21	**7i + 8i**	80	5.5/1
11	MeOOC—	**2j**	19	**7j + 8j**	28	2.5/1
12	$AcNHCH_2$—	**2k**	4	**7k + 8k**	91	4.2/1
13	EtO—	**2l**	4	**7l + 8l**	77	4.4/1
14	$TBSOCH_2$—	**2m**	17	**7m + 8m**	77	5.5/1
15	$TBSOCH_2CH_2$—	**2n**	17	**7n + 8n**	82	4.3/1
16[d]		**2f**	18	**7f + 8f**	46	1/1

[a] 2 equiv of alkynes were used.
[b] Isolated yields.
[c] CH_2Cl_2 was used as a solvent.
[d] The reaction was run in CH_2Cl_2 in the presence of Grubbs 1st generation catalyst (10 mol%).

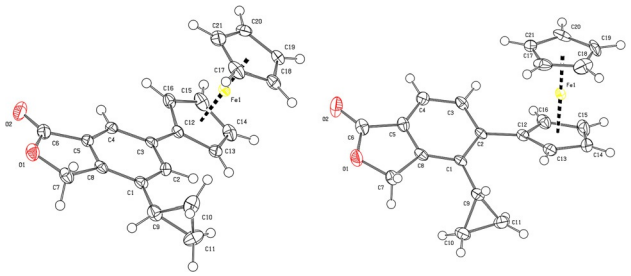
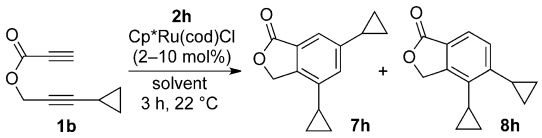


Figure 3. PLATON plot of **7f** (left, yellow crystals) and **8f** (right, red crystals) showing the atom labeling and displacement ellipsoids drawn on 50% probability level.

Table 4. Effect of Cp*Ru(cod)Cl loading and solvent on cyclotrimerization of **1b** with **2h**.



Entry	Catalyst (mol%)	Solvent[a]	T (°C)	Yields (%)[b]	7h/8h
1	10	DCE	22	86	6.5/1
2	5	DCE	22	91	6/1
3	5	DCE	50	97	6/1
4	2	DCE	22	96	6.5/1
5	2	DCE	50	95	6/1
6	10	THF	22	92	6.5/1
7	5	THF	22	97	6/1
8	5	CPME	22	98	8/1
9	5	$CDCl_3$	22	92	6.5/1

[a] DCE = CH_2ClCH_2Cl, CPME = cyclopentyl methyl ether.
[b] 1H NMR yields, internal standard: 1,4-dimethoxybenzene.

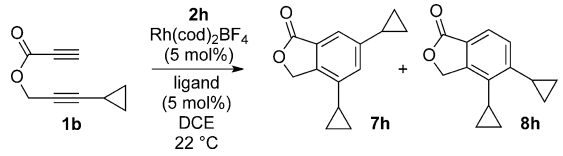
On the other hand, the regioselectivity of the Rh-catalyzed cyclotrimerization seems to be a more complex issue. Examples of the preferential formation of 1,2-[24c,26] or 1,3-[27] regioisomers have been reported. It appears that in each case the corresponding regioselectivity could be the result of a combination of electronic and steric factors, as well as structural features of the linker connecting both triple bonds. These effects by no doubts affect the course of competitive insertion of the alkyne into both Rh–C bonds in the intermediate rhodacycle along with the orientation of the substituent on the alkyne with respect to the rhodium atom.

Although neither theoretical studies addressing these issues nor any detailed studies regarding a ligand effect on the regioselectivity of cyclotrimerization between an unsymmetrically substituted diyne with a terminal alkyne have been published, several reports regarding ligand effect on the course of cyclotrimerization have been described. These involve: a) an effect of a ligand on regioselectvity of homocyclotrimerization catalyzed by Co-,[28a,b] Rh-[28c] and Ir-complexes,[28d] b) on the course of Ir-catalyzed cyclotrimerization of diynes with akynes,[28e,f,g] c) on regioselectivity of Rh-catalyzed reaction of diyne with a disubstituted alkyne,[28h] d) on the rate of a Ni-phosphine complex catalyzed homocyclotrimerization of 1,4-butyndiol,[28i,j] and e) a Rh-catalyzed cyclotrimerization of a symmetrical diyne with a disubstituted alkyne.[28k] A distantly related study deals with the effect of variously substituted Cp′-Rh complexes on co-cyclotrimerization of terminal alkynes with nitriles.[29] Since it has been shown that the ligand environment around the central metal atom in a catalyst can crucially affect reaction yields, rates, regioselectivities, etc.,[30] we decided to explore whether the change of a ligand

could affect not only the yields of the Rh-catalyzed cyclotrimerization but also the regioselectivity.

Once again we decided to use cyclotrimerization of **1b** with cyclopropylethyne **2h** as a model reaction. The complexes were prepared in situ by mixing of $Rh(cod)_2BF_4$ with appropriate phosphine and exposing the mixture to hydrogen prior to the addition of alkynes.[31] The results summarized in Table 5 suggest that the regioselectivity might be dependent on the bite angle of a bidentate ligand. In general, the use of ligands with small (65-93°) or large bite angles (99-108°) provide the product in rather low yields and mostly low regioselectivity (Entries 1-9 and 13-17, respectively). Interestingly in the case of Xanthphos a reversal of the regioselectivity in favor of 1,3-isomer was observed (Entries 16 and 17). Gratifyingly, the use of a ligand with a medium size bite angle (94°), such as dppb, led to a highly selective formation of 1,2-regioisomer **8h** (**7h**/**8h** = 1/12) and also the overall yield of products was considerably increased up to 62% (Entries 10-12). When dppf (99°) and dppp (91°) were used (Entries 5 and 13), still good regioselectivities (**7h**/**8h** = 1/3.5 and 1/3) and reasonable yields (55 and 41%) were obtained. Taking into the account considerably different results obtained for the catalysts possessing BINAP and dppb ligands, despite the fact that both ligands have bite angles of similar values (93 and 94°, respectively) it is obvious that such a difference cannot be explained simply by the bite angle effect and obviously other factors must be involved concomitantly. Besides, the bite angle in a particular complex might take different values depending on an anion, on additional ligands, and also on ligand's coordination modes.[32] Nonetheless, these results clearly indicate that the course of the reaction, that is, regioselectivity and conversion, could be controlled by judicious selection of ligands. Last but not least, it should be mentioned that the activation of the catalytic systems by hydrogen had a positive effect on the reaction rates and yields (compare Entries 6 with 8, 7 with 9, and 10 with 11 and 12).

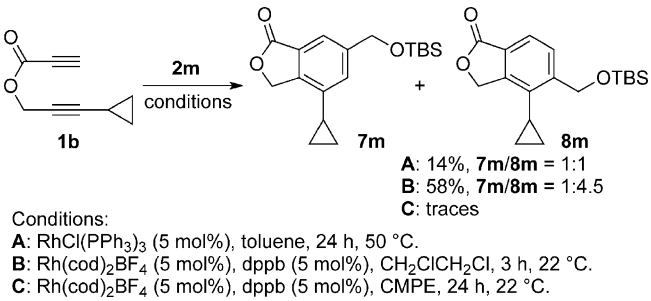
Table 5. Cyclotrimerization of **1b** with various Rh catalysts (5 mol%). Influence of a ligand on **7/8** ratio.



Entry	Ligand	t (h)	β [a]	Yields (%)[b]	**7h**/**8h**
1	Segphos[c]	3	65°	22	1/3
2	dppe[c]	3	86°	16	1/1.3
3	dppe[c]	24	86°	41	1/1.4
4	dppp[c]	3	91°	18	1/3
5	dppp[c]	24	91°	41	1/3
6	BINAP	3	93°	13	nd[d]
7	BINAP	24	93°	15	1/1.8
8	BINAP[c]	3	93°	23	1/1.3
9	BINAP[c]	24	93°	25	1/1.3
10	dppb[c]	3	94°	58	1/12
11	dppb	3	94°	17	1/11
12	dppb	24	94°	62	1/11
13	dppf[c]	3	99°	55	1/3.5
14	DPEPhos[c]	3	104°	16	1/1.4
15	DPEPhos[c]	24	104°	34	1/1.5
16	Xantphos[c]	3	108°	5	1.5/1
17	Xantphos[c]	24	108°	13	1.5/1

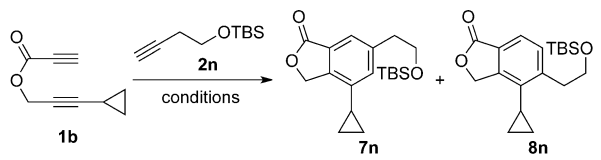
[a] Bite angle. For values see ref. [30].
[b] H NMR yields, internal standard: 1,4-dimethoxybenzene.
[c] Catalyst was activated by H_2.
[d] Regioisomer ratio was not determined.

The above depicted results sparked our interest in exploring a possibility to utilize Rh-complex catalyzed cyclotrimerization for synthesis of **8m** (1,2-regioisomer), a potential advanced intermediate for synthesis of **A** and **B** (Figure 1). Running the reaction in the presence of Wilkinson's catalyst provided 1/1 mixture of **7m** and **8m** in low yield of 14% (Scheme 1). However, using the catalytic system based on a combination of $Rh(cod)_2BF_4$ and dppb not only resulted in increased yield of the desired product (58%) but also in a significantly raised regioselectivity favouring **8m** (**7m**/**8m** = 1/4.5). An attempt to carry out the same reaction in CPME (cyclopentyl methyl ether) provided only traces of the desired product (judged by ^{1}H MNR analysis of the reaction mixture). The low reactivity could probably be attributed to a low solubility of the catalytic system in CPME. The reaction was also performed with unprotected propargyl alcohol **2o** and it proceeded to give the desired products **7o**/**8o** in 72% isolated yield after 3 h reaction time; however in a low 1/1.5 regioisomer ratio.



Scheme 1. Regioselective formation of **8m**.

This catalytic system was also tested for cyclotrimerization of **1b** with the TBS-protected homopropargyl alcohol **2n** (Scheme 2), for compound **8n** could be a precursor of compound **B** (Figure 1). The reaction proceeded as expected to give a mixture of **7n** and **8n**, albeit in a lower but synthetically still interesting



Conditions:
A: $Rh(cod)_2BF_4$ (5 mol%), dppb (5 mol%) DCE, 22 °C.
B: $Rh(cod)_2BF_4$ (5 mol%), dppf (5 mol%) DCE, 22 °C.
C: $Rh(cod)_2BF_4$ (5 mol%), dppp (5 mol%) DCE, 22 °C.
D: $Rh(cod)_2BF_4$ (5 mol%), Segphos (5 mol%) DCE, 22 °C

A: 3 h, 19%,[a] **7n/8n** = 1:2.5
24 h, 23%,[a] **7n/8n** = 1:2
B: 3 h, 64%,[a] **7n/8n** = 1:1.2
C: 3 h, 39%,[a] **7n/8n** = 1:1
24 h, 60%,[a] **7n/8n** = 1:1.3
D: 3 h, 48%,[a] **7n/8n** = 1:1.3
[a] ^{1}H NMR yield.

Scheme 2. Regioselective formation of **8n**.

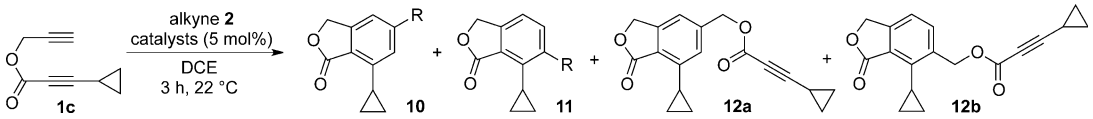
1/2.5 ratio and in a rather low yield of 19% (^{1}H NMR yield). Prolonging the reaction time to 24 h did not have a substantial effect on the yield.

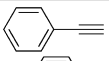
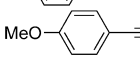
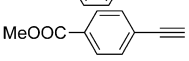
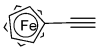
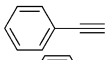
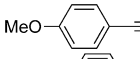
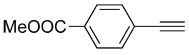
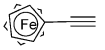
Attempts to improve the selectivity as well as the yield by changing the ligand environment to dppp and dppf were undertaken. The use of the former led to the improvement in yield to 64% (3 h) and the latter to 60% (24 h), but the obtained regioisomer ratios were reduced ~1/1.3. In addition, the reaction catalyzed by $Rh(cod)_2BF_4$ and Segphos was carried out. Although it provided **7n** and **8n** in 48% yield after 3 h, **7n/8n** regioisomer ratio remained as low as 1/1.3.

The above mentioned experiments imply that the ability to control regioselectivity of the cyclotrimerization of unsymmetrically substituted substrates, for example, by changing the ligand, might offer an alternative pathway to important synthetic building blocks.

Finally, we decided to check cyclotrimerization of diyne **1c** possessing inverted positions of the cyclopropyl and ester groups with selected terminal alkynes **2** in the presence of Cp*Ru(cod)Cl and $Rh(cod)_2BF_4$/dppb (Table 6). The catalysis by the Ru-complex proceeded well, and, as expected, 1,3-isomers **10** were obtained as major products. Regioisomer ratios were in general high and the corresponding 7-cyclopropyl-5-(substituted)isobenzofuran-1(3*H*)-ones **10** and 7-cyclopropyl-6-(substituted)isobenzofuran-1(3*H*)-ones **11** were isolated in very good yields

Table 6. Cyclotrimerization of **1c** with various alkynes **2** in the presence of Ru and Rh catalysts.



Entry	Catalyst	Alkyne **2**[a]		t (h)	Products	Yield (%)[b]	**10/11**	**12**, yield(%)[b,c]
1	Cp*Ru(cod)Cl		**2a**	5	**10a + 11a**	59	16/1	13
2			**2b**	7	**10b + 11b**	74	16/1	traces
3			**2d**	25	**10d + 11d**	36	13/1	12
4			**2f**	5	**10f + 11f**	61	7/1	-
5			**2h**	3	**10h + 11h**	65	16/1	-
6		*n*-Bu—	**2i**	2	**10i + 11i**	61	28/1	14
7	$Rh(cod)BF_4$/dppb[d]		**2a**	3	**10a + 11a**	8 (37)[e,f]	1/2	13 (13)[e,f]
8			**2b**	3	**10b + 11b**	13 (43)[e,f]	1/1.3	17 (20)[e,f]
9			**2d**	3	**10d + 11d**	5 (9)[e,g]	1/12	10 (11)[e,g]
10			**2f**	3	**10f + 11f**	21 (25)[e,g,h]	2.5/1	10 (10)[e,g,h]
11			**2h**	3	**10h + 11h**	31 (39)[e,g]	1/5	12 (12)[e,g]
12		*n*-Bu—	**2i**	3	**10i + 11i**	traces (35)[e,f]	1/1.5	– (11)[e,f]

[a] 2 equiv of alkynes were used.
[b] Isolated yields unless otherwise mentioned.
[c] In case of the Ru-catalyzed reactions **12a/12b** ratio was 20:1, whereas for the Rh-catalyzed reaction **12a/12b** = 1:3–4.
[d] Activated by hydrogen.
[e] 1H NMR yields, internal standard: 1,4-dimethoxybenzene.
[f] Yield after 20 h at 50 °C in brackets.
[g] Yield after 24 h in brackets.
[h] At 50 °C.

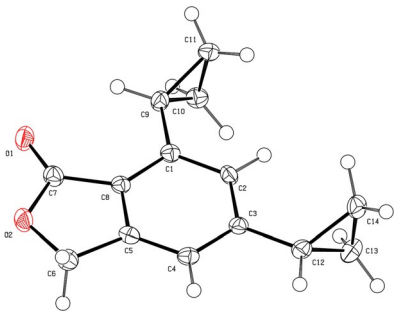


Figure 4. PLATON plot of **10h** showing the atom labeling and displacement ellipsoids drawn on 50% probability level.

(Entries 1-6). The **10**/**11** ratios were in all instances higher than those obtained in the reactions with **1b** under the same reaction conditions (see Table 3). This observation further supports the above mentioned theory[25c] that the more electron deficient the Rh–C bond means slower addition of the terminal alkyne into it. The subsequent X-ray structure analysis of 5,7-dicyclopropylisobenzofuran-1(3*H*)-one **10h** enabled us to unequivocally confirm its structure (Figure 4).

The cyclotrimerization reactions of **1c** catalyzed by the Rh-catalyst proceeded also as expected, giving rise preferentially to 1,2-isomers **11** (Entries 7-12). The obtained regioisomer ratios were rather low, as well as the yields. Some important observations were made from these results, though. Firstly, again, as in the case of the reaction of **1a** with Wilkinson's catalyst, the reaction was slowest with electron-deficient (4-methoxycarbonylphenyl)ethyne **2d**. Also, diyne **1c** was more prone to homocyclotrimerization than **1b** due to the more electron-rich terminal alkyne. And, lastly, in the cyclotrimerization with ferrocenylethyne **2f** the 1,3-regioisomer **11f** was formed as the major product. The same reversal of regioselectivity was again observed for diyne **1a** and Wilkinson's catalyst (see Table 1, Entry 6).

The reaction with cyclopropylethyne **2h** provided the corresponding mixture of **10h** and **11h** in reasonable yields of 31 and 39% after 3 and 24 h, respectively (Entry 11). In this instance the best selectivity was obtained, in favor of 1,2-regioisomer **11h** (**10h**/**11h** = 1/5). An attempt to carry out the reaction of **1c** with cyclopropylethyne **2h** in CPME was undertaken as well, but the reaction did not proceed and the starting diyne remained unreacted (as judged by ^{1}H NMR of the reaction mixture). As in the previous case (Scheme 1, conditions C), a low solubility of the catalytic system could be accounted for that. Finally, the reaction with 1-hexyne **2i** was tried. It did not proceed at 22 °C and had to be executed at 50 °C to obtain the desired products **10i** and **11i** in 35% yield in 1/1.5 ratio after 24 h (Entry 12).

Since the mechanism of the Rh-phosphine complex catalyzed [2+2+2]-cycloaddition reaction of diynes with monoynes was studied by density functional theory (DFT) to support the structural proposal made for the monoyne insertion intermediate,[33] we have also attempted to determine the reaction pathway of $RhCl(PPh_3)_3$ catalyzed cyclotrimerization by means of DFT computations in order to shed light on the course of the reaction. However, despite numerous attempts we were unable to locate a properly defined transition-state structure of the reaction intermediate. Although geometry optimizations starting with the alkyne moiety oriented differently in the initial geometries could always reach chemically plausible geometries, none of these final geometries had a single imaginary vibration in their IR spectra, thus neither of these geometries could be classified as the transition-state structure of the reaction. We thus conclude, that our theoretical model for describing the reaction mechanism of the insertion step was incomplete and the true reaction pathway proceeds apparently in a more complicated way than by a mere cleavage of one of the Rh–C bonds in the rhodacyclopentadiene cycle followed by alkyne insertion. In addition, more complex structures of our substrates (an unsymmetrically substituted diyne, additional functionalities in the linker connecting the triple bond, and hence different electron densities on the triple bonds) could contribute to overall failure of the theoretical calculations. Probably, more sophisticated theoretical models will have to be employed in order to get reliable information; however, such an endeavor is beyond the scope of this study.

Conclusions

A synthetic pathway to 1,2- and 1,3-substituted cyclopropylated benzene derivatives based on cyclotrimerization catalyzed by Ru- and Rh-complexes was explored. The cyclotrimerization catalyzed by Cp*Ru(cod)Cl usually proceeded with good yields of the corresponding products. The preferential formation of 1,3-regioisomers with good regioselectivity ratios ranging from 2.5 to 28/1, depending on the structural features of both substrates, was observed in all cases. The reaction pattern is in agreement with the previously outlined hypothesis.[25] On the other hand, the use of Rh-catalysts proceeded with the preferential formation of 1,2-regioisomers. Unlike the Ru-catalyzed reactions the yields were generally lower as well as the observed regioisomeric ratios. In general, the catalytic activity of the Wilkinson's catalyst ($RhCl(PPh_3)_3$) was low for all the starting diynes used in this study and highly depended on the structure of both substrates. To establish whether the ratio as well as the yields could be improved by varying the ligand

environment around the central rhodium atom, the Rh-catalyzed reaction of **1b** with cyclopropylethyne **2h** was studied in the presence of various ligands. This study clearly showed that both the ratio and the yields can be positively affected by judicious choice of the ligand (dppb): the **7h/8h** ratio was increased from 1/1 to 1/12 and the isolated yield to 62%. Thus, the catalytic system composed of $Rh(cod)_2BF_4$/dppb was then applied for the selective preparation of **8m** - a potential intermediate for the synthesis of **A**. Unfortunately, the use of this catalyst with other substrates was not as successful as expected indicating that this catalytic system is not generally applicable and probably for each pair of reactants, that is, a diyne and an alkyne, a screening of different reaction conditions would have to be performed. Nonetheless, the obtained results indicate that regioselectivity as well as the reaction yield in [2+2+2]-cyclotrimerization can be controlled by changing of the ligand environment around a central metal atom of the catalytically active species.

Experimental Section

For further experimental details, compound characterization, X-ray data,[34] and copies of ^{1}H and ^{13}C NMR data see the supporting information section.

Cyclotrimerization of 1b catalyzed by Cp*Ru(cod)Cl.

A solution of diyne **1b** (37 mg, 0.25 mmol) in dry DCE (4 mL) maintained under an atmosphere of argon was treated with an alkyne **2** (0.5 mmol) and Cp*Ru(cod)Cl (9.7 mg, 0.025 mmol). The reaction mixture was stirred at 22 °C for the time specified in Table 3. Then it was concentrated under reduced pressure and column chromatography of the residue on silica gel (hexanes/Et_2O) provided the corresponding 4-cyclopropyl-3-hydroisobenzofuran-1-ones **7** and **8**.

4-Cyclopropyl-6-phenylisobenzofuran-1(3*H*)-one (7a) and 4-cyclopropyl-5-phenylisobenzofuran-1(3*H*)-one (8a). A colorless crystalline solid, m.p. = 115.4 °C (recrystallized from DCM/hexanes). **7a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91–7.90 (m, 1H), 7.58–7.55 (m, 2H), 7.48–7.43 (m, 3H), 7.42–7.41 (m, 1H), 5.41 (s, 2H), 1.87 (tt, J = 8.5, 5.2 Hz, 1H), 1.11–1.07 (m, 2H), 0.86–0.83 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 144.7, 143.1, 139.8, 138.7, 129.0, 128.9, 128.0, 127.2, 126.0, 121.2, 69.0, 12.0, 7.8. **8a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 1H), 7.46–7.44 (m, 1H, overlapped), 7.42–7.37 (m, 5H), 5.42 (s, 2H), 1.94 (tt, J = 8.5, 5.7 Hz, 1H), 0.77–0.73 (m, 2H), 0.27–0.24 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 148.8, 148.1, 140.3, 131.6, 134.4, 129.1, 128.1, 127.6, 124.4, 123.4, 69.3, 11.7, 7.4. **7a+8a**: IR (KBr) ν_{max} 3078, 3052, 3004, 1760, 1595, 1479, 1452, 1344, 1230, 1066, 1054, 1027, 1009, 946, 764 cm^{-1}; MS (CI) *m/z* 251 [$(M+H\cdot)^+$, 100%], 252 (18), 250 ($M^{+\cdot}$, 69), 221 (26), 207 (8), 178 (11), 165 (6), 152 (4), 115 (3); HRMS (CI) *m/z* $(M+H\cdot)^+$ calcd for $C_{17}H_{15}O_2$ 251.1072, found 251.1074. R_f (8:2 hexanes/EtOAc) = 0.45.

4-Cyclopropyl-6-(4-methoxyphenyl)isobenzofuran-1(3*H*)-one (7b) and 4-cyclopropyl-5-(4-methoxyphenyl)isobenzofuran-1(3*H*)-one (8b). A yellowish crystalline solid, m.p. = 121–122 °C (recrystallized from DCM/hexanes). **7b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, J = 1.3 Hz, 1H), 7.52–7.49 (m, 2H), 7.38 (d, J = 1.1 Hz, 1H), 7.01–6.98 (m, 2H), 5.41 (s, 2H), 3.86 (s, 3H), 1.85 (tt, J = 8.4, 5.2 Hz, 1H), 1.10–1.06 (m, 2H), 0.85–0.82 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 159.7, 144.1, 142.7, 138.5, 130.4, 128.5, 128.3, 126.0, 120.7, 114.4, 69.1, 55.4, 12.0, 7.8. **8b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.37–7.34 (m, 2H), 7.00–6.96 (m, 2H), 5.41 (s, 2H), 3.88 (s, 3H), 1.93 (tt, J = 8.7, 6.0 Hz, 1H), 0.80–0.76 (m, 2H), 0.28–0.24 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 159.2, 148.5, 148.3, 134.2, 132.6, 132.2, 131.6, 124.0, 123.4, 113.5, 69.3, 55.3, 11.7, 7.6. **7b+8b**: IR (KBr) ν_{max} 3078, 3001, 2953, 2932, 2836, 1757, 1607, 1521, 1488, 1251, 1183, 1069, 1039, 1018, 949, 830, 776 cm^{-1}; MS (EI) *m/z* 280 ($M^{+\cdot}$, 100%), 281 (20), 251 (42), 223 (9), 178 (11), 165 (19), 152 (10), 115 (9), 44 (23); HRMS (ESI) *m/z* $(M+H\cdot)^+$ calcd for $C_{18}H_{17}O_3$ 281.1172, found 281.1173. R_f (8:2 hexanes/EtOAc) = 0.35.

4-Cyclopropyl-6-[4-(trifluoromethyl)phenyl]isobenzofuran-1(3*H*)-one (7c) and 4-cyclopropyl-5-[4-(trifluoromethyl)-phenyl]isobenzofuran-1(3*H*)-one (8c). A brownish crystalline solid, m.p. = 180–181 °C (recrystallized from DCM/hexanes). **7c**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 1.1 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 1.2 Hz, 1H), 5.43 (s, 2H), 1.89 (tt, J = 8.4, 5.2 Hz, 1H), 1.14–1.10 (m, 2H), 0.87–0.83 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 145.6, 143.3, 141.6, 139.2, 130.1 (q, J = 32.6 Hz), 128.9, 127.6, 126.3, 125.9 (q, J = 3.5 Hz), 121.4, 69.1, 12.0, 7.9 (CF_3 group is overlapped). **8c**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 5.43 (s, 2H), 1.94 (tt, J = 8.4, 5.8 Hz, 1H), 0.80–0.76 (m, 2H), 0.27–0.23 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 148.2, 147.2, 144.0, 131.4, 134.6, 129.5, 129.8 (q, J = 32.6 Hz), 123.7, 125.1 (q, J = 3.5 Hz), 123.2, 69.3, 11.6, 7.5 (CF_3 group overlapped). **7c+8c**: IR (KBr) ν_{max} 3084, 3013, 2926, 2851, 1775, 1757, 1613, 1485, 1329, 1177, 1117, 1072, 1036, 1018, 845, 776 cm^{-1}; MS (CI) *m/z* 319 [$(M+H\cdot)^+$, 100%], 320 (18), 318 ($M^{+\cdot}$, 77), 299 (34), 289 (33), 275 (8), 246 (5), 191 (4), 165 (2), 115 (1); HRMS (CI) *m/z* $(M+H\cdot)^+$ calcd for $C_{18}H_{14}O_2F_3$ 319.0946, found 319.0948. R_f (8:2 hexanes/EtOAc) = 0.36.

Methyl 4-(7-cyclopropyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)benzoate (7d) and methyl 4-(4-cyclopropyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)benzoate (8d). A yellow crystalline solid, m.p. = 147.3 °C (recrystallized from DCM/hexanes). **7d**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13–8.11 (m, 2H), 7.93 (d, J = 1.4 Hz, 1H), 7.64–7.62 (m, 2H), 7.44 (d, J = 1.3 Hz, 1H), 5.43 (s, 2H), 3.95 (s, 3H), 1.88 (tt, J = 8.4, 5.2 Hz, 1H), 1.12–1.09 (m, 2H), 0.87–0.84 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 166.7, 145.5, 144.1, 142.0, 139.0, 130.3, 129.7, 128.9, 127.2, 126.3, 121.5, 69.1, 52.2, 12.0, 7.9. **8d**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13–8.10 (m, 2H), 7.82 (d, J = 7.9 Hz, 1H), 7.51–7.48 (m, 2H), 7.44 (d, J = 8.0 Hz, 1H), 5.43 (s, 2H), 3.96 (s, 3H), 1.94 (tt, J = 8.6, 5.8 Hz, 1H), 0.77–0.74 (m, 2H), 0.25–0.22 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 166.8, 148.3, 147.7, 145.0, 134.5, 131.4, 129.4, 129.2, 125.1, 123.6, 69.3, 52.2, 11.6, 7.5 (one signal is overlapped).

7d+8d: IR (KBr) ν_{max} 3066, 3013, 2956, 1757, 1718, 1601, 1434, 1353, 1278, 1227, 1180, 1105, 1066, 1015, 952, 863, 767 cm^{-1}; MS (EI) *m/z* 308 (M^+, 100), 309 (21), 279 (90), 265 (20), 205 (12), 191 (24), 178 (12), 165 (23), 152 (9), 115 (7), 59 (11), 44 (14); HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_{19}H_{16}O_4Na$ 331.0941, found 331.0942. R_f (8:2 hexanes/EtOAc) = 0.26.

4-(7-Cyclopropyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-benzonitrile (7e) and 4-(4-cyclopropyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)benzonitrile (8e). A brownish crystalline solid, m.p. = 213.8 °C (recrystallized from DCM/hexanes, then from MeOH). **7e**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 1.5 Hz, 1H), 7.77–7.75 (m, 2H), 7.68–7.66 (m, 2H), 7.40 (d, J = 1.5 Hz, 1H), 5.44 (s, 2H), 1.89 (tt, J = 8.4, 5.2 Hz, 1H), 1.14–1.10 (m, 2H), 0.87–0.84 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 146.0, 144.2, 141.1, 139.4, 132.8, 128.8, 127.9, 126.5, 121.5, 118.6, 111.8, 69.1, 12.0, 8.0. **8e**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 1H), 7.77–7.73 (m, 2H), 7.57–7.53 (m, 2H), 7.41 (d, J = 7.8 Hz, 2H), 5.42 (s, 2H), 2.00–1.89 (m, 1H), 0.82–0.74 (m, 2H), 0.26–0.19 (m, 2H). ^{13}C NMR signals intensity was too low to be assigned. **7e+8e**: IR (KBr) ν_{max} 3090, 3007, 2953, 2929, 2217, 1766, 1607, 1488, 1443, 1362, 1180, 1066, 1009, 949, 842, 770 cm^{-1}; MS (EI) *m/z* 275 (M^+, 74), 276 (16), 246 (100), 232 (25), 217 (12), 203 (35), 190 (29), 177 (13), 165 (6), 151 (7), 140 (12), 115 (15), 63 (7), 44 (21); HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_{18}H_{13}O_2NNa$ 298.0839, found 298.0840. R_f (8:2 hexanes/EtOAc) = 0.36.

4-Cyclopropyl-6-ferrocenylisobenzofuran-1(3*H*)-one (7f) and 4-cyclopropyl-5-ferrocenylisobenzofuran-1(3*H*)-one (8f). 7f: A yellow crystalline solid, m.p. = 151.1 °C (recrystallized from DCM/hexanes). ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 1.2 Hz, 1H), 7.29 (d, J = 1.1 Hz, 1H), 5.34 (s, 2H), 4.67–4.65 (m, 2H), 4.36–4.34 (m, 2H), 4.03 (s, 5H), 1.82 (tt, J = 8.4, 5.2 Hz, 1H), 1.09–1.05 (m, 2H), 0.82–0.79 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 143.4, 141.8, 138.0, 127.7, 125.8, 119.8, 84.2, 70.1, 69.8, 69.2, 67.0, 11.9, 7.8. **8f**: A red crystalline solid, m.p. = 179.4 °C (recrystallized from DCM/hexanes). ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 5.35 (s, 2H), 4.63–4.62 (m, 2H), 4.38–4.37 (m, 2H), 4.10 (s, 5H), 1.89–1.83 (m, 1H), 0.87–0.83 (m, 2H), 0.26–0.22 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 148.5, 146.9, 134.2, 132.4, 122.9, 122.6, 85.2, 71.03, 70.1, 69.3, 68.8, 11.9, 8.1. **7f+8f:** IR (KBr) ν_{max} 3093, 3004, 2923, 1757, 1515, 1449, 1347, 1308, 1224, 1066, 1012, 952, 842, 779, 486 cm^{-1}; MS (EI) *m/z* 358 (M^+, 100), 359 (25), 191 (9), 178 (6), 165 (10), 121 (18), 56 (4); HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_{21}H_{18}O_2FeNa$ 381.0548, found 381.0547. R_f (8:2 hexanes/EtOAc) = 0.38.

4-Cyclopropyl-6-(trimethylsilyl)isobenzofuran-1(3*H*)-one (7g) and 4-cyclopropyl-5-(trimethylsilyl)isobenzofuran-1(3*H*)-one (8g). A colorless amorphous solid. **7g**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.88–7.87 (m, 1H), 7.35–7.34 (m, 1H), 5.36 (s, 2H), 1.82 (tt, J = 8.5, 5.2 Hz, 1H), 1.06–1.02 (m, 2H), 0.80–0.77 (m, 2H), 0.28 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 146.6, 142.6, 137.2, 134.5, 127.8, 124.7, 69.1, 11.9, 7.4, −1.2. **8g**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 5.37 (s, 2H), 2.08 (tt, J = 8.6, 5.8 Hz, 1H), 1.04–1.01 (m, 2H), 0.76–0.73 (m, 2H), 0.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 148.9, 145.1, 142.8, 135.7, 126.4, 122.4, 69.8, 15.1, 7.5, 0.6. **7g+8g**: IR (KBr) ν_{max} 3072, 3025, 3004, 2947, 2893, 1763, 1446, 1350, 1293, 1251, 1108, 1072, 1018, 952, 890, 839, 758 cm^{-1}; MS (EI) *m/z* 246 (M^+, 20), 247 (3), 231 (100), 157 (8), 128 (13), 115 (8), 73 (14), 49(19); HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_{14}H_{18}O_2SiNa$ 269.0968, found 269.0970. R_f (8:2 hexanes/EtOAc) = 0.54.

4,6-Dicyclopropylisobenzofuran-1(3*H*)-one (7h) and 4,5-dicyclopropylisobenzofuran-1(3*H*)-one (8h). A yellowish oil. **7h**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 1.4 Hz, 1H), 5.31 (s, 2H), 1.93 (tt, J = 8.4, 5.0 Hz, 1H), 1.77 (tt, J = 8.4, 5.2 Hz, 1H), 1.03–0.99 (m, 4H), 0.77–0.74 (m, 2H), 0.72–0.69 (m, 2H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 146.2, 143.1, 137.8, 128.4, 124.7, 118.7, 69.0, 15.3, 11.8, 9.6, 7.6. **8h**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 5.35 (s, 2H), 2.46 (tt, J = 8.5, 5.3 Hz, 1H), 1.98–1.95 (m, 1H), 1.13–1.10 (m, 2H), 1.07–1.04 (m, 2H), 0.79–0.76 (m, 2H), 0.69–0.66 (m, 2H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 151.2, 146.8, 135.3, 125.5, 123.7, 122.7, 69.2, 13.4, 10.8, 9.7, 6.3. **7h+8h**: IR (KBr) ν_{max} 3081, 3010, 2947, 2869, 1763, 1500, 1464, 1356, 1284, 1096, 1012, 958, 937, 773 cm^{-1}; MS (CI) *m/z* 215 [$(M+H\cdot)^+$, 100%], 216 (15), 214 (M^+, 36), 185 (23), 171 (5), 155 (4), 129 (6), 115 (7); HRMS (CI) *m/z* $(M+H\cdot)^+$ calcd for $C_{14}H_{15}O_2$ 215.1072, found 215.1070. R_f (8:2 hexanes/EtOAc) = 0.41.

6-Butyl-4-cyclopropylisobenzofuran-1(3*H*)-one (7i) and 5-butyl-4-cyclopropylisobenzofuran-1(3*H*)-one (8i). A brownish oil. **7i**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J = 0.8 Hz, 1H), 7.00 (d, J = 0.8 Hz, 1H), 5.32 (s, 2H), 2.66–2.63 (m, 2H), 1.77 (tt, J = 8.4, 5.2 Hz, 1H), 1.60–1.54 (m, 2H), 1.32 (sext, J = 7.4 Hz, 2H), 1.03–1.00 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H), 0.76–0.73 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 144.7, 143.4, 137.9, 130.2, 125.4, 122.1, 69.0, 35.3, 33.5, 22.1, 13.8, 11.8, 7.6. **8i**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 5.34 (s, 2H), 2.93–2.90 (m, 2H), 1.87–1.81 (m, 1H), 1.63–1.60 (m, 2H), 1.41 (sext, J = 7.4 Hz, 2H), 1.04–1.01 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H), 0.62–0.59 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 150.6, 147.1, 134.4, 130.5, 123.5, 123.2, 69.3, 32.9, 32.8, 22.8, 13.9, 10.8, 6.1. **7i+8i:** IR (KBr) ν_{max} 3004, 2956, 2926, 2872, 2857, 1772, 1497, 1461, 1320, 1281, 1147, 1063, 1015, 955, 770 cm^{-1}; MS (CI) *m/z* 231 [$(M+H\cdot)^+$, 100%], 232 (17), 230 (M^+, 45), 202 (18), 188 (11), 159 (5), 129 (6), 115 (5); HRMS (CI) *m/z* $(M+H\cdot)^+$ calcd for $C_{15}H_{19}O_2$ 231.1385, found 231.1386. R_f (8:2 hexanes/EtOAc) = 0.51.

Methyl 7-cyclopropyl-3-oxo-1,3-dihydroisobenzofuran-5-carboxylate (7j) and methyl 4-cyclopropyl-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (8j). A colorless amorphous solid. **7j**: ^1H NMR (600 MHz, $CDCl_3$) δ 8.36 (d, J = 1.1 Hz, 1H), 7.87–7.86 (m, 1H), 5.43 (s, 2H), 3.95 (s, 3H), 1.82 (tt, J = 8.4, 5.1 Hz, 1H), 1.13–1.09 (m, 2H), 0.88–0,84 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 165.9, 149.9, 139.1, 132.1, 130.4, 125.9, 124.3, 69.1, 52.5, 11.8, 8.3. **8j**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 5.41 (s, 2H), 3.97 (s, 3H), 2.16 (tt, J = 8.6, 5.8 Hz, 1H), 1.03–1.00 (m, 2H), 0.55–0.52 (m, 2H). ^{13}C NMR intensity of signals was too low to be assigned. **7j+8j**: IR (KBr) ν_{max} 3084, 3007, 2950, 2851, 1763, 1727, 1625, 1592, 1437, 1302, 1251, 1224, 1192, 1066, 1015, 949, 761 cm^{-1}; MS (EI) *m/z* 232 (M^+, 27), 233 (4), 201 (100), 189 (20), 173 (14), 145 (11), 128 (25), 115 (62), 83 (27), 77 (39),

44 (14); HRMS (CI) *m/z* $(M+H\cdot)^+$ calcd for $C_{13}H_{13}O_4$ 233.0814, found 233.0815. R_f (8:2 hexanes/EtOAc) = 0.23.

***N*-[(7-Cyclopropyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-methyl]acetamide (7k) and *N*-[(4-cyclopropyl-1-oxo-1,3-dihydroisobenzofuran-5-yl)methyl]acetamide (8k).** A colorless crystalline solid, m.p. = 120.3 °C (recrystallized from DCM/hexanes). **7k**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.12 (s, 1H), 6.58 (bs, 1H), 5.29 (s, 2H), 4.43 (d, J = 6.0 Hz, 2H), 2.02 (s, 3H), 1.75 (tt, J = 8.4, 5.2 Hz, 1H), 1.04–1.00 (m, 2H), 0.76–0.73 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 170.3, 144.9, 140.7, 138.7, 129.4, 125.5, 121.2, 69.1, 42.9, 23.1, 11.8, 7.9. **8k**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 5.31 (s, 2H), 6.40 (bs, 1H), 4.71 (d, J = 5.8 Hz, 2H), 2.06 (s, 3H), 1.88 (d, J = 6.0 Hz, 1H), 1.86 (tt, J = 8.4, 6.0 Hz, 1H), 1.07–1.04 (m, 2H), 0.64–0.61 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2, 170.3, 146.9, 145.5, 134.6, 128.8, 124.5, 123.8, 69.4, 41.0, 29.6, 10.5, 6.1. **7k+8k**: IR (KBr) ν_{max} 3300, 3084, 3001, 2938, 1754, 1640, 1562, 1497, 1452, 1317, 1287, 1153, 1072, 1030, 1012, 776 cm^{-1}; MS (EI) *m/z* 245 (M^+, 89), 246 (16), 203 (63), 188 (82), 158 (22), 144 (24), 128 (26), 115 (35), 91 (23), 84 (16), 49 (31), 43 (100); HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_{14}H_{15}O_3NNa$ 268.0944, found 268.0945. R_f (3:7 hexanes/EtOAc) = 0.20.

4-Cyclopropyl-6-ethoxyisobenzofuran-1(3*H*)-one (7l) and 4-cyclopropyl-5-ethoxyisobenzofuran-1(3*H*)-one (8l). A colorless crystalline solid, m.p. = 85.0 °C (recrystallized from DCM/hexanes). **7l**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (d, J = 2.1 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 5.30 (s, 2H), 4.03 (q, J = 7.0 Hz, 2H), 1.74 (tt, J = 8.4, 5.1 Hz, 1H), 1.41 (t, J = 7.0 Hz, 3H), 1.03–0.99 (m, 2H), 0.76–0.73 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 160.4, 139.7, 138.4, 126.4, 118.8, 105.0, 69.0, 63.9, 14.6, 11.8, 8.0. **8l**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 5.29 (s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 1.73 (tt, J = 5.6 Hz, 1H), 1.47 (t, J = 7.0 Hz, 3H), 0.95–0.91 (m, 2H), 0.80–0.77 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 162.7, 147.7, 125.0, 124.7, 117.4, 112.6, 68.7, 64.5, 14.7, 8.1, 5.6. **7l+8l**: IR (KBr) ν_{max} 3081, 3016, 2983, 2932, 1763, 1745, 1625, 1500, 1458, 1377, 1335, 1290, 1239, 1165, 1084, 1069, 1042, 949, 863, 773 cm^{-1}; MS (EI) *m/z* 218 (M^+, 90), 219 (14), 189 (100), 175 (20), 161 (97), 147 (30), 133 (28), 115 (30), 105 (33), 77 (31), 49 (47); HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_{13}H_{14}O_3Na$ 241.0835, found 241.0835. R_f (8:2 hexanes/EtOAc) = 0.43.

6-[(*tert*-Butyldimethylsilyl)oxymethyl]-4-cyclopropylisobenzofuran-1(3*H*)-one (7m) and 5-[(*tert*-butyldimethylsilyl)oxymethyl]-4-cyclopropylisobenzofuran-1(3*H*)-one (8m). A colorless crystalline solid, m.p. = 135.1 °C (recrystallized from DCM/hexanes). **7m**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.19 (s, 1H), 5.36 (s, 2H), 4.77 (s, 2H), 1.79 (tt, J = 8.4, 5.2 Hz, 1H), 1.06–1.03 (m, 2H), 0.94 (s, 9H), 0.79–0.76 (m, 2H), 0.10 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 144.7, 143.6, 138.2, 127.4, 125.4, 120.1, 69.0, 64.4, 25.9, 18.4, 11.8, 7.9, −5.3. **8m**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 5.37 (s, 2H), 4.99 (s, 2H), 1.92 (tt, J = 8.3, 5.9 Hz, 1H), 1.03–0.99 (m, 2H), 0.97 (s, 9H), 0.62–0.59 (m, 2H), 0.14 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 148.6, 146.2, 132.7, 127.4, 124.4, 123.9, 69.3, 62.4, 25.9, 18.4, 10.1, 5.8, −5.4. **7m+8m**: IR (KBr) ν_{max} 2950, 2926, 2884, 2857, 1772, 1461, 1356, 1263, 1138, 1102, 1087, 1063, 1018, 955, 860, 836, 779 cm^{-1}; MS (EI) *m/z* 303 [$(M\text{-}Me\cdot)^+$, 2%], 261 (100), 231 (73), 187 (18), 159 (13), 143 (12), 128 (17), 115 (18), 91 (8), 75 (57), 57 (19), 41 (14); HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_{18}H_{26}O_3SiNa$ 341.1543, found 341.1544. R_f (8:2 hexanes/EtOAc) = 0.49.

6-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-4-cyclopropylisobenzofuran-1(3*H*)-one (7n) and 5-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}-4-cyclopropylisobenzofuran-1(3*H*)-one (8n). A yellowish oil. **7n**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.08 (s, 1H), 5.35 (s, 2H), 3.80 (t, J = 6.6 Hz, 2H), 2.86 (t, J = 6.6 Hz, 2H), 1.78 (tt, J = 8.4, 5.2 Hz, 1H), 1.04–1.00 (m, 2H), 0.85 (s, 9H), 0.78–0.75 (m, 2H), −0.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 143.9, 141.4, 137.8, 131.2, 125.4, 123.0, 69.0, 64.0, 39.2, 25.8, 18.2, 11.8, 7.6, −5.5. **8n**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 5.36 (s, 2H), 3.87 (t, J = 6.8 Hz, 2H), 3.19 (t, J = 6.8 Hz, 2H), 1.88 (tt, J = 8.4, 5.9 Hz, 1H), 1.07–1.04 (m, 2H), 0.84 (s, 9H), 0.66–0.63 (m, 2H), −0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 147.0, 147.0, 135.3, 131.4, 123.8, 123.5, 69.4, 63.4, 36.4, 25.8, 18.3, 10.9, 6.3, −5.5. **7n+8n**: IR (KBr) ν_{max} 2953, 2929, 2881, 2854, 1769, 1473, 1461, 1359, 1254, 1144, 1099, 1066, 1018, 836, 776 cm^{-1}; MS (EI) *m/z* 317 [$(M\text{-}Me\cdot)^+$, 2%], 275 (100), 245 (69), 201 (7), 171 (11), 128 (8), 115 (5), 75 (23), 57 (7), 41 (5); HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_{19}H_{28}O_3SiNa$ 355.1700, found 355.1701. R_f (8:2 hexanes/EtOAc) = 0.55.

4-Cyclopropyl-6-(hydroxymethyl)isobenzofuran-1(3*H*)-one (7o) and 4-Cyclopropyl-5-(hydroxymethyl)isobenzofuran-1(3*H*)-one (8o). A white crystalline solid, m.p. = 75.6 °C (recrystallized from DCM/hexanes). **7o**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.21 (s, 1H), 5.32 (s, 2H), 4.72 (s, 2H), 2.68 (bs, 1H), 1.77 (tt, J = 8.4, 5.1 Hz, 1H), 1.05–1.01 (m, 2H), 0.79–0.76 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 145.1, 143.1, 138.5, 128.3, 125.3, 120.6, 69.2, 64.3, 11.8, 7.9. **8o**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 5.33 (s, 2H), 4.99 (s, 2H), 2.68 (bs, 1H), 1.84 (tt, J = 8.5, 5.8 Hz, 1H), 1.06–1.01 (m, 2H), 0.63–0.59 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 148.1, 146.5, 133.6, 128.0, 124.4, 123.8, 69.4, 62.2, 10.2, 5.8. **7o+8o**: IR (KBr) ν_{max} 3461, 3007, 2914, 1745, 1452, 1428, 1374, 1353, 1263, 1144, 1063, 1012, 949, 848, 776 cm^{-1}; MS (EI) *m/z* 204 (M^+, 53%), 205 (7), 175 (100), 161 (13), 147 (10), 129 (20), 115 (27), 91 (22), 77 (11); HRMS (EI) *m/z* M^+ calcd for $C_{12}H_{12}O_3$ 204.0786, found: 204.0787. R_f (7:3 hexanes/EtOAc) = 0.11.

Cyclotrimerization of 1c catalyzed by Cp*Ru(cod)Cl.

A solution of diyne **1c** (37 mg, 0.25 mmol) in dry DCE (4 mL) maintained under an atmosphere of argon was treated with an alkyne **2** (0.5 mmol) and Cp*Ru(cod)Cl (4.8 mg, 0.0125 mmol). The reaction mixture was stirred at 22 °C for the time specified in Table 6. Then it was concentrated under reduced pressure and column chromatography of the residue on silica gel (hexanes/EtOAc) provided the corresponding 7-cyclopropyl-3-hydroisobenzofuran-1-ones **10** and **11**.

7-Cyclopropyl-5-phenylisobenzofuran-1(3*H*)-one (10a) and 7-cyclopropyl-6-phenylisobenzofuran-1(3*H*)-one (11a). A brownish crystalline solid, m.p. = 137.5 °C (recrystallized from DCM/hexanes). **10a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57–7.54 (m, 2H), 7.49–7.45 (m, 2H), 7.43–7.40 (m, 1H),

7.37–7.36 (m, 1H), 7.04–7.03 (m, 1H), 5.28 (s, 2H), 3.22 (tt, J=8.5, 5.1 Hz, 1H), 1.22–1.18 (m, 2H), 0.90–0.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 147.7, 147.4, 147.0, 140.0, 129.0, 128.4, 127.4, 121.9, 121.8, 117.0, 68.6, 11.0, 10.0. **11a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51–7.29 (m, 7H), 5.27 (s, 2H), 2.21 (tt, J=8.7, 5.8 Hz, 1H), 0.87–0.84 (m, 2H), 0.23–0.19 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 146.5, 144.2, 141.7, 140.6, 136.1, 129.4, 129.0, 128.0, 127.2, 125.8, 119.6, 68.2, 11.0, 9.6. **10a+11a**: IR (KBr) ν_{max} 3081, 3058, 3007, 2926, 1742, 1607, 1470, 1353, 1201, 1063, 1006, 890, 764, 698 cm^{-1}; MS (EI) m/z 250 ($M^{+\cdot}$, 100%), 235 (15), 205 (65), 191 (24), 178 (22), 165 (19), 152 (8), 115 (6), 89 (4), 63 (4); HRMS (EI) m/z $M^{+\cdot}$ calcd for $C_{17}H_{14}O_2$ 250.0994, found: 250.0996. R_f (8:2 hexanes/EtOAc)=0.39.

7-Cyclopropyl-5-(4-methoxyphenyl)isobenzofuran-1(3*H*)-one (10b) and 7-cyclopropyl-6-(4-methoxy-phenyl)isobenzofuran-1(3*H*)-one (11b). A yellowish crystalline solid, m.p.=119.3°C (recrystallized from DCM/hexanes). **10b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H), 7.33–7.32 (m, 1H), 7.01–6.97 (m, 2H), 6.99–6.98 (m, 1H), 5.26 (s, 2H), 3.85 (s, 3H), 3.19 (tt, J=8.4, 5.1 Hz, 1H), 1.20–1.16 (m, 2H), 0.89–0.85 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 160.0, 147.8, 147.0, 146.9, 132.3, 128.5, 121.3, 121.2, 116.4, 114.4, 68.6, 55.4, 10.9, 10.0. **11b**: ^{1}H NMR intensity of signals was too low to be assigned. ^{13}C NMR intensity of signals was too low to be assigned. **10b+11b**: IR (KBr) ν_{max} 3040, 3010, 2962, 2839, 1745, 1604, 1524, 1446, 1251, 1183, 1054, 1036, 1006, 824 cm^{-1}; MS (EI) m/z 280 ($M^{+\cdot}$, 100%), 281 (25), 265 (13), 235 (42), 205 (10), 178 (11), 165 (12), 152 (7), 115 (5), 89 (3); HRMS (EI) m/z $M^{+\cdot}$ calcd for $C_{18}H_{16}O_3$ 280.1099, found: 280.1101. R_f (8:2 hexanes/EtOAc)=0.29.

Methyl 4-(7-cyclopropyl-1-oxo-1,3-dihydroisobenzo-furan-5-yl)benzoate (10d) and methyl 4-(4-cyclopropyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)benzoate (11d). A yellow crystalline solid, m.p.=194.8°C (recrystallized from DCM/hexanes). **10d**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13–8.10 (m, 2H), 7.63–7.60 (m, 2H), 7.41–7.39 (m, 1H), 7.05–7.03 (m, 1H), 5.29 (s, 2H), 3.94 (s, 3H), 3.21 (tt, J=8.5, 5.2 Hz, 1H), 1.23–1.19 (m, 2H), 0.90–0.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 166.6, 147.8, 147.4, 146.2, 144.4, 130.2, 130.0, 127.4, 122.6, 122.0, 117.2, 68.6, 52.2, 11.1, 10.0. **11d**: ^{1}H NMR intensity of signals was too low to be assigned. ^{13}C NMR intensity of signals was too low to be assigned. **10d+11d**: IR (KBr) ν_{max} 3093, 2947, 2872, 1751, 1718, 1604, 1446, 1290, 1269, 1222, 1120, 1060, 1009, 857, 776 cm^{-1}; MS (EI) m/z 308 ($M^{+\cdot}$, 100%), 308 (21), 293 (13), 277 (11), 263 (33), 205 (23), 189 (13), 165 (8), 115 (4); HRMS (EI) m/z $M^{+\cdot}$ calcd for $C_{19}H_{16}O_4$ 308.1049, found: 308.1051. R_f (8:2 hexanes/EtOAc)=0.20.

7-Cyclopropyl-5-ferrocenylisobenzofuran-1(3*H*)-one (10f) and 7-cyclopropyl-6-ferrocenylisobenzofuran-1(3*H*)-one (11f). An orange crystalline solid, m.p.=211.1°C (recrystallized from DCM/hexanes). **10f**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (s, 1H), 6.92 (s, 1H), 5.23 (s, 2H), 4.67–4.64 (m, 2H), 4.41–4.38 (m, 2H), 4.04 (s, 5H), 3.16 (tt, J=8.4, 5.1 Hz, 1H), 1.21–1.16 (m, 2H), 0.87–0.83 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 147.5, 146.9, 146.3, 120.5, 120.3, 115.4, 83.3, 69.9, 69.8, 68.4, 67.1, 10.8, 9.8. **11f**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J=7.8 Hz, 1H), 7.28 (d, J=7.8 Hz, 1H), 5.20 (s, 2H), 4.56 (s, 2H), 4.34 (s, 2H), 4.10 (s, 5H), 2.04 (tt, J=8.6, 5.7 Hz, 1H), 0.98–0.92 (m, 2H), 0.19–0.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 145.5, 141.6, 141.3, 137.0, 125.6, 119.0, 86.1, 70.8, 69.6, 68.2, 68.1, 11.4, 10.1. **10f+11f**: IR (KBr) ν_{max} 3096, 3075, 2929, 1742, 1613, 1449, 1350, 1207, 1045, 1006, 806 cm^{-1}; MS (EI) m/z 358 ($M^{+\cdot}$, 100%), 359 (26), 191 (8), 178 (10), 165 (16), 152 (10), 121 (55), 56 (13); HRMS (EI) m/z $M^{+\cdot}$ calcd for $C_{21}H_{18}O_2Fe$ 358.0656, found: 358.0655. R_f (8:2 hexanes/EtOAc)=0.32.

5,7-Dicyclopropylisobenzofuran-1(3*H*)-one (10h) and 6,7-dicyclopropylisobenzofuran-1(3H)-one (11h). A white crystalline solid, m.p.=112.6°C (recrystallized from DCM/hexanes). **10h**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.56 (s, 1H), 5.16 (s, 2H), 3.11 (tt, J=8.4, 5.2 Hz, 1H), 1.92 (tt, J=8.4, 5.0 Hz, 1H), 1.15–1.10 (m, 2H), 1.07–1.03 (m, 2H), 0.81–0.77 (m, 2H), 0.75–0.72 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 151.7, 147.6, 146.3, 120.5, 120.4, 114.5, 68.4, 16.1, 10.7, 10.4, 9.7. **11h**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, J=7.9 Hz, 1H), 7.11 (d, J=8.0 Hz, 1H), 5.16 (s, 2H), 2.44 (tt, J=8.5, 5.4 Hz, 1H), 2.05 (tt, J=8.6, 5.7 Hz, 1H), 1.22–1.17 (m, 2H), 1.09–1.05 (m, 2H), 0.76–0.71 (m, 2H), 0.70–0.67 (m, 2H). ^{13}C NMR intensity of signals was too low to be assigned. **10h+11h**: IR (KBr) ν_{max} 3087, 3007, 2929, 2866, 1739, 1613, 1440, 1350, 1201, 1069, 1006, 985, 872, 695 cm^{-1}; MS (EI) m/z 214 ($M^{+\cdot}$, 93%), 215 (16), 199 (22), 185 (13), 169 (66), 155 (64), 141 (51), 128 (89), 115 (87), 84 (45), 63 (22), 49 (100), 35 (47); HRMS (EI) m/z $M^{+\cdot}$ calcd for $C_{14}H_{14}O_2$ 214.0994, found: 214.0993. R_f (8:2 hexanes/EtOAc)=0.34.

5-Butyl-7-cyclopropylisobenzofuran-1(3*H*)-one (10i) and 6-butyl-7-cyclopropylisobenzofuran-1(3*H*)-one (11i). A white crystalline solid, m.p.=41.2°C (recrystallized from DCM/hexanes). **10i**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.64 (s, 1H), 5.19 (s, 2H), 3.13 (tt, J=8.5, 5.1 Hz, 1H), 2.65–2.61 (m, 2H), 1.61–1.54 (m, 2H), 1.34 (sext, 7.4 Hz, 2H), 1.15–1.11 (m, 2H), 0.92 (t, J=7.3 Hz, 3H), 0.81–0.78 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 150.1, 147.5, 146.4, 122.9, 120.7, 118.1, 68.4, 36.1, 33.4, 22.3, 13.8, 10.8, 9.7. **11i**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J=7.8 Hz, 1H), 7.22 (d, J=7.8 Hz, 1H), 5.16 (s, 2H), 2.94–2.90 (m, 2H), 1.93 (tt, J=8.6, 5.8 Hz, 1H), 1.62–1.57 (m, 2H), 1.42–1.36 (m, 2H), 1.20–1.16 (m, 2H), 0.95 (t, J=7.3 Hz, 3H), 0.66–0.63 (m, 2H). ^{13}C NMR intensity of signals was too low to be assigned. **10i+11i**: IR (KBr) ν_{max} 3078, 2956, 2926, 2863, 1751, 1607, 1455, 1329, 1207, 1045, 1012, 991, 943, 692 cm^{-1}; MS (EI) m/z 230 ($M^{+\cdot}$, 100%), 231 (18), 215 (16), 185 (43), 173 (50), 143 (24), 129 (37), 115 (27), 91 (8), 77 (5); HRMS (EI) m/z $M^{+\cdot}$ calcd for $C_{15}H_{18}O_2$ 230.1307, found: 230.1310. R_f (8:2 hexanes/EtOAc)=0.49.

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