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Ruthenium-Catalyzed Cycloaddition of 1,6-Diynes and Nitriles under Mild Conditions: Role of the Coordinating Group of Nitriles

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Abstract: In the presence of a catalytic amount of [Cp*RuCl(cod)] (Cp* = pentamethylcyclopentadienyl, cod = 1,5-cyclooctadiene), 1,6-diynes were allowed to react chemo- and regioselectively with nitriles bearing a coordinating group, such as dicyanides or α-halonitriles, at ambient temperature to afford bicyclic pyridines. Careful screening of nitrile components revealed that a C≡C triple bond or heteroatom substituents, such as methoxy and methylthio groups, proved to act as the coordinating groups, whereas C=C or C=O double bonds and amino groups failed to promote cycloaddition. This suggests that coordinating groups with multiple π-bonds or lone pairs are essential for the nitrile components.

Keywords: alkynes · cycloaddition · nitriles · pyridine · ruthenium catalysis

Introduction

Pyridine is one of the most important nitrogen heterocycles, playing a key role in several biological processes.[1] Pyridines are also used extensively for ligands in organometallic chemistry.[2] Although substituted pyridine rings have been constructed generally through conventional condensation methods, such as the Hantzsch synthesis,[1] the transition-metal-mediated [2+2+2] cyclocotrimerization of two alkynes with a nitrile is an alternative atom-economical method to produce multiply substituted pyridines under neutral and mild conditions.[3] The cyclocotrimerizations have been explored extensively since their discovery by Wakatsuki and Yamazaki,[4] and catalytic, partially intramolecular approaches utilizing α,ω-diynes or cyanoalkynes proved to be particularly useful for the assembly of bicyclic pyridine frameworks, as pioneered by Vollhardt and co-workers.[5] However, the chemo- and regioselectivity, as well as reaction conditions of catalytic protocols, must be improved before these methods can be compared with stoichiometric methods.[6] In this context, mild and highly selective cycloadditions of α,ω-diynes with nitriles were achieved recently by using a chiral indenylcobalt catalyst and a nickel *N*-heterocyclic carbene complex.[7]

We developed independently the ruthenium-catalyzed cycloadditions of 1,6-diynes with carbon–heteroatom multiple bonds, and found that carbon–nitrogen triple bonds directly connecting to an electron-withdrawing group are capable of participating in the ruthenium-catalyzed cycloaddition at 60–80 °C.[8] This is in striking contrast to simple acetonitrile or benzonitrile that yield hardly any cycloadducts. Quite surprisingly, however, dicyanides bearing two cyano groups at remote positions reacted with 1,6-diynes even at ambient temperature under the ruthenium catalysis.[9] Notably, the cycloaddition took place at one of the two cyano groups, resulting in the formation of pyridines possessing an intact cyanoalkyl side chain after completion of the reaction.

After our reports, Saá and co-workers revisited the ruthenium-catalyzed cycloadditions of 1,6-diynes with electron-deficient nitriles or dicyanides by means of a different catalytic system, [Cp*Ru(CH_3CN)$_3$]PF_6/Et_4NCl, to broaden the scope of the substrates.[10] Interestingly, they reported that the dicyanides play a critical role in cleaving a dimeric complex, [{Cp*Ru(CH_3CN)Cl}$_2$], generated in situ from the cationic precatalyst and Et_4NCl. Also encouraging is that some nitriles possessing a heteroatom element in close proximity to the cyano group exhibited a similar reactivity with malononitrile to give the corresponding pyridines, albeit with

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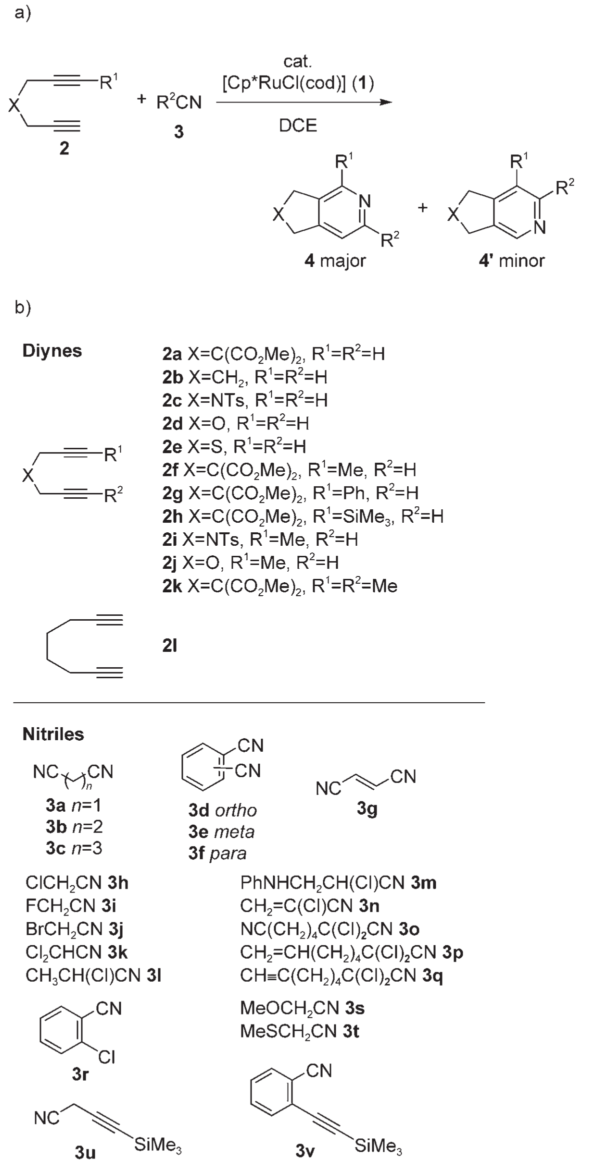
moderate yields of around 50%. This report shows that further explorations of the scope of substrate, as well as the reaction mechanism, are required to establish the generality of the ruthenium-catalyzed pyridine formation. Herein, we report results that provide a plausible explanation for the role of the coordinating group on the nitrile component.

Results and Discussion

Ruthenium-catalyzed cycloaddition of dicyanides: To achieve a selective and efficient pyridine formation, we employed a neutral ruthenium(II) complex, [Cp*RuCl(cod)] (**1**), having both an electron-donating planar ligand (Cp* = pentamethylcyclopentadienyl) and a readily leaving supporting ligand (cod = 1,5-cyclooctadiene), as this proved to be an efficient precatalyst for the cycloaddition of the α,ω-diynes with alkenes,[11] alkynes,[12] isocyanates and isothiocyanates,[13] or tricarbonyl compounds.[14] The reaction of dimethyl dipropargylmalonate (**2a**) and two equivalents of acetonitrile in the presence of 1 mol% **1** in 1,2-dichloroethane (DCE) at room temperature (around 25 °C), however, gave only a mixture of dimers and trimers of **2a**. Diyne **2a** was recovered quantitatively if the reaction was carried out with acetonitrile as a solvent. On the other hand, **2a** was allowed to react with 1.5 equivalents of malononitrile (**3a**) in the presence of 2 mol% **1** in DCE at room temperature for 22 h to afford bicyclic pyridine **4aa** in 92% yield (Scheme 1, Table 1, run 1). The reaction reached completion after 7 h at 60 °C and a similar yield (91%) of **4aa** was isolated (run 2). As a precatalyst, a Ru^{III} complex, [(Cp*RuCl$_2$)$_2$], was found to be less effective, furnishing **4aa** in 22% yield (2 mol%, RT, 22 h). In striking contrast, [RuCl$_2$(cod)(CH$_3$CN)$_2$] or [Ru(C$_6$Me$_6$)(cod)] were totally incompetent for pyridine formation under the same reaction conditions.

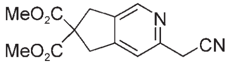
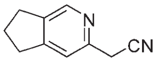
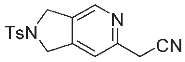
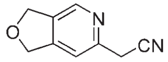
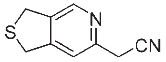
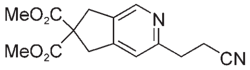
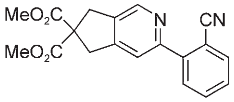
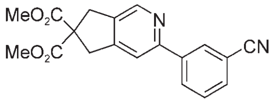
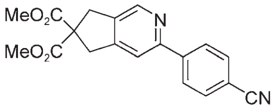
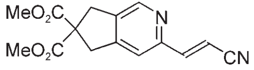
A similar reaction of parent 1,6-heptadiyne (**2b**) with **3a** at ambient temperature for 16 h gave **4ba** in 77% yield, indicating that the assistance of the *gem*-disubstituent effect (Thorpe–Ingold effect) is not essential (Table 1, run 3).[15] In contrast, 1,7-octadiyne proved to be totally ineffective for the present ruthenium catalysis (run 4). The use of *N*,*N*-dipropargyltosylamide (**2c**) and propargyl ether (**2d**) led to the formation of pyridine-fused heterocycles **4ca** and **4da** in 85 and 86% yield, respectively (runs 5 and 6). The ruthenium complex was also capable of catalyzing the cycloaddition of dipropargyl sulfide (**2e**) with **3a** even at room temperature (run 7). The desired sulfur heterocycle **4ea** was obtained in 63% yield, although an increased catalyst loading of 5 mol% was required.



Scheme 1. a) Ruthenium-catalyzed cycloaddition of diynes **2** with nitriles **3**. b) Diynes and nitriles employed in this study.

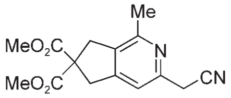
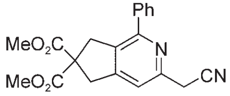
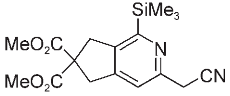
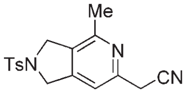
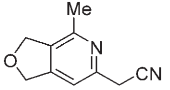
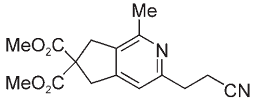
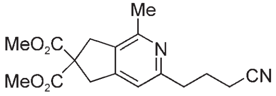
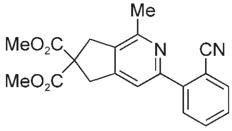
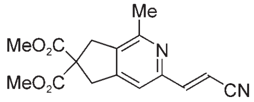
To examine the generality in terms of the nitrile component, several other dicyanides were then subjected to the catalyzed cycloaddition with diyne **2a**. A tether unit connecting the two cyano groups has a decisive effect upon the chemoselectivity. Succinonitrile (**3b**), in which the two cyano groups are separated by two methylene units, gave **4ab** in only 29% yield, along with the concomitant formation of a mixture of dimer and trimer of **2a** (Table 1, entry 8). These results clearly suggest that the shorter tether favored the desired pyridine formation. The yield of **4ab** was, however, improved to 62% with increased loadings of ruthenium complex **1** (5 mol%) and dicyanide **3b** (4 equiv) as a result of the partial inhibition of the diyne dimerization (run 9). In contrast to **3b**, dicyanides connecting a more rigid tether gave better results. For example, *ortho*-, *meta*-, and *para*-dicyanobenzenes **3d**–**3f** were allowed to react with **2a**, delivering the corresponding pyridines **4ad**–**4af** in 43–61% yield (runs 10–12). In these cases, the product yields appeared to depend on the distance between the two cyano groups. On the other hand, fumaronitrile (**3g**), in which two cyano groups are in a mutual *trans* relationship, gave acrylonitrile derivative **4ag** in a much higher yield (88%, entry

Table 1. Cycloaddition of diynes with dicyanides.

Run	**2**,**3**	**1** [mol %]	T [°C]	t [h]	Product, Yield [%]
1	**2a**,**3a**	2	RT	22	**4aa**, 92 
2	**2a**,**3a**	2	60	7	**4aa**, 91
3	**2b**,**3a**	2	RT	16	**4ba**, 77 
4	**2l**,**3a**	5	RT	24	no reaction
5	**2c**,**3a**	2	RT	0.5	**4ca**, 85 
6	**2d**,**3a**	2	RT	14	**4da**, 86 
7	**2e**,**3a**	5	RT	24	**4ea**, 63 
8	**2a**,**3b**	2	RT	18	**4ab**, 29 
9	**2a**,**3b**[a]	5	RT	12	**4ab**, 62
10	**2a**,**3d**	2	RT	4	**4ad**, 61 
11	**2a**,**3e**	2	RT	7	**4ae**, 50 
12	**2a**,**3f**	2	RT	17	**4af**, 43 
13	**2a**,**3g**	2	RT	22	**4ag**, 88 

[a] Four equivalents.

Table 2. Cycloaddition of unsymmetrical diynes with dicyanides.

Run	**2**,**3**	**1** [mol %]	T [°C]	t [h]	Product, Yield [%] [**4**:**4′**][a]
1	**2f**,**3a**	5	RT	24	**4fa**, 44[b] [100:0] 
2	**2f**,**3a**	2	60	5	**4fa**, 97 [95:5]
3	**2g**,**3a**	10	60	24	**4ga**, 78[c] [100:0] 
4	**2h**,**3a**	5	60	5.5	**4ha**, 92 [100:0] 
5	**2i**,**3a**	2	60	0.5	**4ia**, 95 [100:0] 
6	**2j**,**3a**	2	60	16	**4ja**, 97 [95:5] 
7	**2f**,**3b**	2	RT	10	**4fb**, 83 [100:0] 
8	**2f**,**3c**	5	RT	22	**4fc**, 46 [100:0] 
9	**2f**,**3d**	2	RT	7	**4fd**, 89 [100:0] 
10	**2f**,**3g**	5	RT	24	**4fg**, 89 [100:0] 

[a] The isomer ratio was determined by ^{1}H NMR spectroscopy. [b] Diyne **2f** was recovered in 40% yield. [c] Diyne **2g** was recovered in 11% yield.

13) than that for phthalonitrile (**3d**) possessing a *cis* dicyanide moiety (61%, entry 10).

The following experiments disclosed that the exceptional reactivity of the dicyanides is not attributed simply to the electron-withdrawing ability of the cyano group. In place of malononitrile (**3a**) or terephthalonitrile (**3f**), methyl cyanoacetate or methyl *p*-cyanobenzoate, in which an ester group substitutes one of the cyano groups in **3a** or **3f**, were employed, however, the corresponding bicyclic pyridines were formed in less than 10% yield at ambient temperature.

We next turned our attention to the regioselectivity of the cycloaddition of unsymmetrical 1,6-diynes and dicyanides.[8b] The cycloaddition of malonate derivative **2f** possessing a methyl terminal and malononitrile **3a** was first conducted at ambient temperature (Table 2, run 1). The reaction did not, however, complete within 24 h, even with an increased catalyst loading of 5 mol%. As a result, the yield of **4fa** is moderate, albeit with excellent regioselectivity, and 40% of the diyne was recovered intact. At elevated temperature (60°C), the cycloaddition uneventfully reached completion within 5 h in the presence of 2 mol% **1** to give **4fa** in 97% yield, although the regioselectivity was lowered to 95:5 (run 2). The reaction of conjugated diyne **2g** bearing a phenyl terminal turned out to be very slow, even under the heating conditions. Upon increasing the catalyst loading to 10 mol%, cycloadduct **4ga** was obtained as a single regioisomer in 78% yield with 11% recovery of **2g** (run 3).

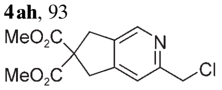
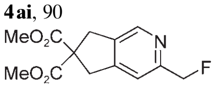
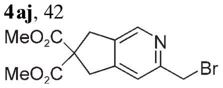
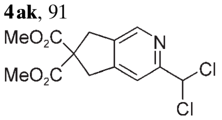
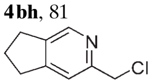
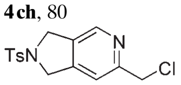
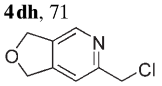
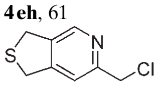
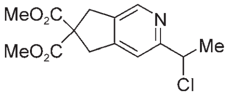
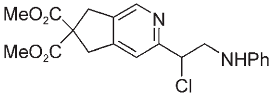
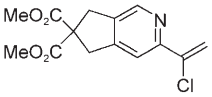
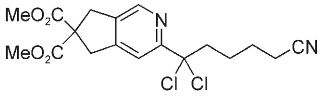
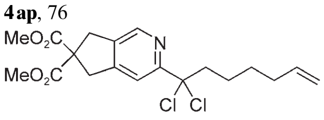
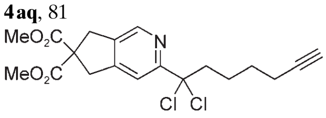
With 5 mol% loading of **1**, sterically demanding trimethylsilyl-substituted diyne **2h** underwent cycloaddition for 5.5 h at the same temperature to give **4ha** as a single regioisomer in 92% yield (run 4). Similarly, aza and oxa heterocycles **4ia** and **4ja** were obtained in high yields and regioselectivity (runs 5 and 6).

In contrast to malononitrile, succinonitrile (**3b**) underwent a clean reaction with **2f** at ambient temperature in the presence of 2 mol% **1** to afford **4fb** as a single regioisomer in 83% yield (run 7). This shows that the terminal methyl substituent considerably retarded the undesirable dimerization of **2f** (Table 1, run 7). However, the reaction of a dicyanide having a longer tether, glutaronitrile (**3c**), suffered from the competitive dimerization of **2f**, resulting in the lower yield of **4fc** (run 8). Rigid dicyanides **3d** and **3g** were also converted regioselectively to the corresponding pyridines in good yields (runs 9 and 10).

Exploratory study on the scope of nitrile components: In striking contrast to the above dicyanides, monocyanides, such as acetonitrile or methyl cyanoacetate, gave poor results. In addition, one of the two cyano groups in the dicyanides remained intact after the completion of pyridine formation. This suggests that one cyano moiety might behave as a coordinating group assisting the cycloaddition of the other cyano group. Thus, other nitriles possessing a heteroatom-coordinating group α to the cyano group were screened to expand the scope of the nitrile substrate. As mentioned, Saá and co-workers reported that chloroacetonitrile (**3h**) was allowed to react with diyne **2a** in the presence of 10 mol% [Cp*Ru(CH_3CN)$_3$]PF_6/Et_4NCl in DMF at room temperature for 1.5 h to give chloromethylpyridine **4ah** in 56% yield.[10] Under our standard conditions, the same product was obtained in 93% yield (Table 3, run 1). Under similar conditions, fluoroacetonitrile (**3i**) furnished **4ai** in 90% yield (run 2), whereas the corresponding bromide **4aj** was obtained from bromoacetonitrile (**3j**) in only moderate yield, probably due to its instability (run 3). Because **3j** is an activated halide, oxidative addition of its C–Br bond to Ru species might give catalytically inactive species that lead to the decreased yield. α,α-Dichloroacetonitrile **3k** also exhibited a similarly good reactivity and the corresponding product **4ak** was obtained in a high yield (run 4). These results are in striking contrast to that observed for trichloroacetonitrile, which failed to undergo cycloaddition within 24 h at ambient temperature, even with an increased catalyst loading of 5 mol%, although the corresponding cycloadduct was obtained at an elevated temperature of 80 °C.[8] Moreover, β-chloronitriles, such as 3-chloropropionitrile and *o*-chlorobenzonitrile (**3r**, see below) gave no cycloadduct under the same reaction conditions. Therefore, both the number and the position of halogen substitution on the nitrile component proved to play important roles.

To establish the generality of the α-halonitrile cycloaddition, various combinations of diynes and nitriles were examined, as summarized in Table 3. The high-yield formation of **4bh** from 1,6-heptadiyne (**2b**) again shows that the assistance of the *gem*-disubstituent effect is not essential (run 5).[15] The use of *N*,*N*-dipropargyltosylamide (**2c**), dipropargyl ether (**2d**), and dipropargylsulfide (**2e**) afforded pyridine-

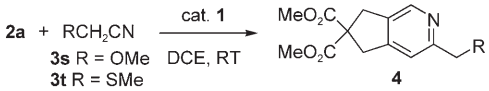
Table 3. Cycloaddition of diynes with α-halonitriles.[a]

Run	2,3	1 [mol%]	*t* [h]	Product, Yield [%]
1	**2a,3h**	2	2	**4ah**, 93 
2	**2a,3i**	2	1	**4ai**, 90 
3	**2a,3j**	2	3	**4aj**, 42 
4	**2a,3k**	2	3	**4ak**, 91 
5	**2b,3h**	2	6	**4bh**, 81 
6	**2c,3h**	2	4	**4ch**, 80 
7	**2d,3h**	2	20	**4dh**, 71 
8	**2e,3h**	5	20	**4eh**, 61 
9	**2a,3l**	2	4	**4al**, 87 
10	**2a,3m**	2	6	**4am**, 71 
11	**2a,3n**	2	2	**4an**, 87 
12	**2a,3o**	2	10	**4ao**, 84 
13	**2a,3p**	2	24	**4ap**, 76 
14	**2a,3q**	2	24	**4aq**, 81 

[a] All reactions were carried out at RT.

fused heterocycles **4ch**, **4dh**, and **4eh**, respectively, in 61–80 % yield, indicative of the ruthenium catalysis being compatible with heteroatom tethers (runs 6–8). In terms of the nitrile component, 2-chloropropionitrile (**3l**) and its amino analogue **3m** or 2-chloroacrylonitrile (**3n**) underwent uneventful cycloaddition with **2a** at ambient temperature for 2–6 h to give pyridines **4al**, **4am**, or **4an**, respectively, in good yields (runs 9–11). In the case of dicyanide **3o**, the cycloaddition took place exclusively at the cyano group α to the dichloromethylene moiety (run 12). Notably, selective pyridine formations were observed for α,α-dichloronitriles **3p** and **3q** bearing an alkene or an alkyne terminal (runs 13 and 14), whereas these unsaturated α,α-dichloronitriles are capable of undergoing transition-metal-catalyzed atom-transfer radical cyclization.[16]

In addition to these halonitriles, nitriles bearing an oxygen, a nitrogen, or a sulfur substituent were subjected to cycloaddition with **2a** (Scheme 2). In the presence of 2 mol % **1**, methoxyacetonitrile (**3s**) was allowed to react with **2a** at ambient temperature for 17 h to obtain the desired cycloadduct **4as**, albeit in low yield. In this case, the dimer of **2a** was also formed as major product in 40 % yield. To suppress the undesired dimerization, a large excess of **3s** (10 equiv) was used with an increased catalyst loading. As a consequence, the reaction reached completion within 3 h, and the yield of **4as** was improved to 70 %. In a similar manner, except for catalyst loading of 20 mol %, methylthioacetonitrile (**3t**) underwent cycloaddition with **2a** for 24 h to afford **4at** in 32 % yield along with the diyne dimer (31 %).

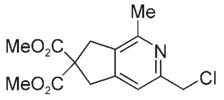
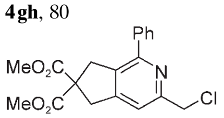
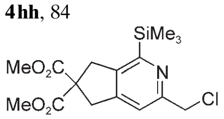
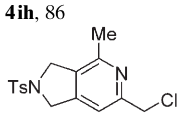
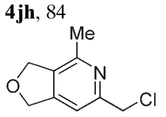
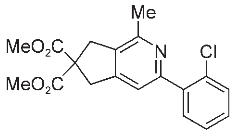
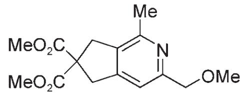
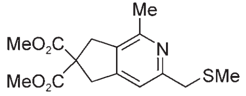


1 [mol%]	**3**, equiv	*t* [h]	**4**, yield [%]
2	**3s**, 1.5	17	**4as**, 23
5	**3s**, 10	3	**4as**, 70
20	**3t**, 10	24	**4at**, 32

Scheme 2. Cycloaddition of diyne **2a** with methoxyacetonitrile **3s** and methylthioacetonitrile **3t**.

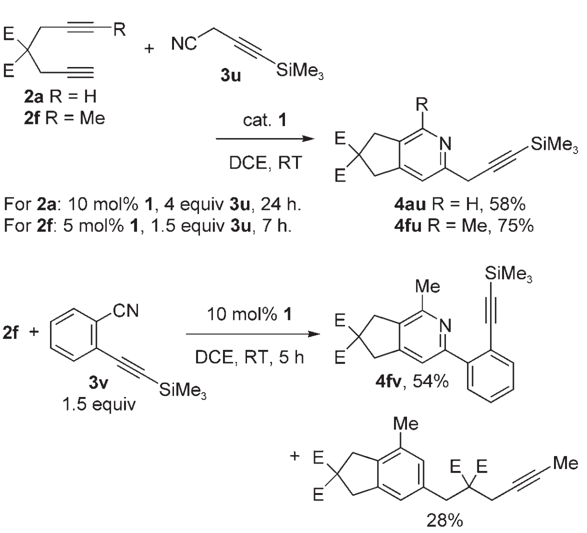
The cycloaddition of chloroacetonitrile (**3h**) with the unsymmetrical diynes turned out to be more effective than that of the dicyanides. As described above, the reaction of methyl-substituted diyne **2f** with malononitrile did not complete within 24 h at ambient temperature. Upon heating at 60 °C, the desired product was obtained in an excellent yield, although the regioselectivity was slightly decreased relative to that at room temperature (Table 2, runs 1 and 2). In contrast, the reaction of **2f** and **3h** uneventfully reached completion within 3 h at room temperature, and gratifyingly, the desired pyridine **4fh** was obtained in 88 % yield as a sole regioisomer (Table 4, run 1). The reactions with other diynes **2g** and **2h** bearing a bulky terminal substituent also proceeded at ambient temperature to afford **4gh** and **4hh** in 80 and 84 % yield, respectively (runs 2 and 3). The heteroatoms on the tether chains have no detrimental effect on the regioselectivity (runs 4 and 5). Moreover, the significant aspect of the cycloaddition of these unsymmetrical diynes is that their self-dimerization is inhibited by the steric repulsion of the terminal substituent. In fact, *o*-chlorobenzonitrile (**3r**) proved to be an incompetent nitrile component toward the cycloaddition with **2a**, resulting in the exclusive formation of the dimer of **2a**. On the other hand, **3r** was capable of undergoing cycloaddition with **2f** to furnish **4fr** in 71 % yield (run 6). Similarly, methoxyacetonitrile (**3s**) and methylthioacetonitrile (**3t**) were converted to the corresponding pyridines **4fs** and **4ft** in 79 and 81 % yield, respectively, without increased loadings of these nitriles (runs 7 and 8).

Table 4. Cycloaddition of unsymmetrical diynes with halo-, methoxy-, and methylthionitriles.[a]

Run	2,3	**1** [mol %]	*t* [h]	Product, Yield [%][b]
1	**2f**,**3h**	2	3	**4fh**, 88 
2	**2g**,**3h**	5	6	**4gh**, 80 
3	**2h**,**3h**	5	4	**4hh**, 84 
4	**2i**,**3h**	2	3	**4ih**, 86 
5	**2j**,**3h**	2	15	**4jh**, 84 
6	**2f**,**3r**	5	8	**4fr**, 71 
7	**2f**,**3s**	2	10	**4fs**, 79 
8	**2f**,**3t**	5	24	**4ft**, 81 

[a] All reactions were carried out at RT. [b] All products were obtained as single regioisomers.

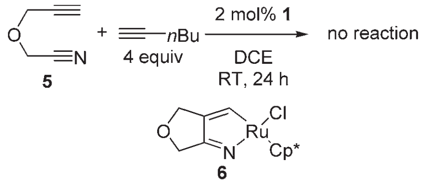
Reaction mechanism: the role of the coordinating group of nitrile components: In striking contrast to α-halo-, α-methoxy-, or α-methylthionitriles, acetonitriles possessing a nitrogen substituent, such as *N,N*-dimethylaminoacetonitrile or *N*-methylaminoacetonitrile, gave no corresponding cycloadducts. This indicates that multiple lone pairs are required for the ruthenium-catalyzed cyclocotrimerization. On the basis of these results, one might consider that highly nucleophilic amino groups deactivated the ruthenium catalysis through their strong coordination. This possibility can be ruled out, however, because the cycloadducts of diynes and dicyanides, the less-nucleophilic cyanoalkylpyridine, also failed to undergo the second cycloaddition with the intact cyano group, although the first cycloaddition was not inhibited by the accumulating pyridine product. In addition, α-chloronitrile possessing an amino group **3m** underwent clean cycloaddition at ambient temperature to give the corresponding cycloadduct **4am**. This means that an amino group does not inhibit the catalytic formation of pyridine. In addition, the incompetence of cyanoesters compared to dicyanides also suggests the importance of the multiple π-bonds for the assisting group.[17–19] On the other hand, Saá and co-workers suggested that the dicyanides cleave a dimeric complex, $[\{Cp^*Ru(CH_3CN)Cl\}_2]$, through the coordination to both ruthenium centers with their nitrogen lone pairs to form a catalytically active species.[10] With these facts in mind, we examined the possibility of a C≡C triple bond as an assisting group. However, in our ruthenium-catalyzed cycloaddition, terminal alkynes generally show much higher reactivity than simple nitriles. Thus, the C≡C triple bond should be sterically shielded by a bulky terminal group to inhibit the unfavorable reaction on the alkyne moiety. To this end, monocyanide **3u** possessing a trimethylsilyl-substituted alkyne moiety (4 equiv) reacted with **2a** in the presence of 10 mol % **1** at ambient temperature (Scheme 3). Gratifyingly, the expected pyridine **4au** was obtained, albeit in moderate yield (58 %). Moreover, unsymmetrical diyne **2f** was allowed to react with 1.5 equivalents of **3u** with a lower catalyst loading of 5 mol %, resulting in the regioselective formation of **4fu** in 75 % yield. Another nitrile substrate *o*-alkynylbenzonitrile **3v**, in which the alkynyl and cyano groups are connected with a phenylene tether, was also allowed to react with **2f** in a similar manner to afford **4fv** in 54 % yield, along with the dimer of **2f** in 28 % yield (Scheme 3), although no cycloadduct was obtained from **2a** with **3v**. As expected, the reaction of diyne **2a** with *trans*-3-pentenenitrile resulted in the formation of the diyne dimer in 60 % yield. These results clearly indicated that the cycloaddition of **3u** and **3v** proceeds with the assistance of the 4e-η^2-coordination with the carbon–carbon triple bond.[20,21] Therefore, the cycloaddition ability of the dicyanides must be attributed to the carbon–nitrogen triple bond, rather than to the nitrogen lone pair.



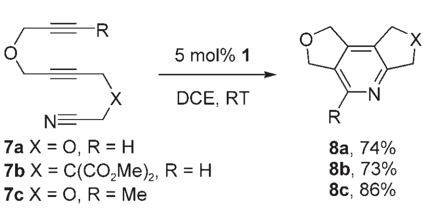
For **2a**: 10 mol% **1**, 4 equiv **3u**, 24 h.
For **2f**: 5 mol% **1**, 1.5 equiv **3u**, 7 h.

Scheme 3. Ruthenium-catalyzed cycloaddition of **2a** and **2f** with cyanoalkyne **3u** and **3v** (E = CO_2Me).

It has been considered that the ruthenium-catalyzed cycloadditions proceed via a ruthenacyclopentatriene intermediate, on the basis of theoretical calculations, as well as the isolation of bicyclic analogues of such a ruthenacycle.[8b,12b–d,i,22] An alternative possibility is that the intermediacy of an azaruthenacyclopentadiene may account for the unusual observations mentioned above. The reaction of α-propargyloxyacetonitrile **5** with excess 1-hexyne, however, gave no cycloadduct, which rules out the catalytic pathway via the azaruthenacyclopentadiene intermediate, such as **6**, to the pyridine product (Scheme 4). This was also supported by the fact that cyanodiyne **7a** bearing both a 1,6-diyne moiety and a pendant nitrile was converted successfully to tricyclic pyridine **8a** in 74 % yield by means of a slow-addition technique (syringe-pump addition of **7a** over 3 h, then stirring for 24 h), as well as a high-dilution condition (0.01 M solution), avoiding bimolecular side reactions (Scheme 5). Notably, the oxygen atom α to the C≡N triple bond is not imperative for the completion of intramolecular cyclization. In the same manner, cyanodiyne with a malonate tether **7b**



Scheme 4. Failed cycloaddition of cyanoalkyne **5** with 1-hexyne.

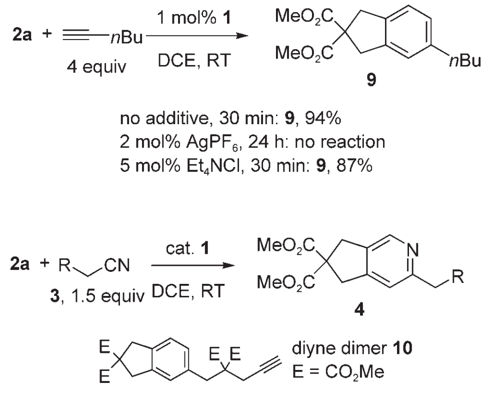


For **7a**,**b**: addition through syringe pump over 3 h, then stirring for 24 h.
For **7c**: addition through syringe over 15 min, then stirring for 1 h.

Scheme 5. Ruthenium-catalyzed cyclization of cyanodiyne **7**.

gave **8b** in a comparable yield. In contrast to **7a** and **7b**, **7c** possessing no terminal alkyne requires neither the slow-addition technique nor a high-dilution condition. With a catalyst loading of 5 mol %, **7c** was selectively converted to **8c** in 86 % yield within 1 h at ambient temperature. To the best of our knowledge, these are the first examples of a fully intramolecular [2+2+2] cyclocotrimerization of alkynes with a nitrile.

To obtain further insight into the mechanism, we conducted the chlorine-ligand-abstraction experiments outlined in Scheme 6. It was found previously that the cationic ruthenium species produced in situ from **1** and a silver salt is totally ineffective for the intramolecular alkyne cyclotrimerization.[12c] This is probably attributed to the $[Cp^*Ru]^+$ fragment capable of forming a stable arene complex.[12c] The deteriorative effect of the formation of cationic species was reproduced by conducting the cycloaddition of **2a** with 1-hexyne in the presence of 1 mol % **1** and 2 mol % $AgPF_6$. Under these conditions, no reaction took place even after 24 h, whereas in the absence of the silver salt the cycloaddition completed within 30 min to give **9** in 94 % yield.



no additive, 30 min: **9**, 94%
2 mol% $AgPF_6$, 24 h: no reaction
5 mol% Et_4NCl, 30 min: **9**, 87%

3a R = CN
2 mol% **1**, no additive, 22 h: **4aa**, 92%
5 mol% **1**, 10 mol% $AgPF_6$, 24 h: **4aa**, 64%

3h R = Cl (2 mol% **1**)
no additive, 2 h: **4ah**, 93%
4 mol% $AgPF_6$, 24 h: **4ah**, 78%
5 mol% Et_4NCl, 18 h: **4ah**, 68% + **10**, 14%
10 mol% Et_4NCl, 16 h: **4ah**, 74% + **10**, 12%
20 mol% Et_4NCl, 24 h: **4ah**, 69% + **10**, 15%

3s R = OMe
2 mol% **1**, no additive, 17 h: **4as**, 23%
10 mol% **1**, 20 mol% $AgPF_6$, 24 h: **4as**, 45%

Scheme 6. Effects of additives on ruthenium-catalyzed cycloadditions.

On the other hand, the cycloaddition of the same diyne with malononitrile (**3a**) proceeded in the presence of the silver salt. Thus, upon treatment with 5 mol % **1** and 10 mol % $AgPF_6$ at room temperature for 24 h, pyridine **4aa** was obtained in 64 % yield. These experiments revealed that the chlorine ligand is not essential for the pyridine formation. The cationic system still functions in the cycloaddition of the dicyanide, albeit with diminished efficiency, because the pyridine produced behaves as a readily removable η^1-nitrogen ligand toward the $[Cp^*Ru]^+$ fragment. This is in striking contrast to the arene product, giving the stable η^6-arene complex. The decrease in catalytic efficiency was not so pronounced for chloroacetonitrile (**3h**), giving a higher product yield with a smaller catalyst loading. Notably, the cycloaddition of only 1.5 equivalents of methoxyacetonitrile (**3s**) selectively afforded **4as** in moderate yield under the cationic conditions, preventing the dimerization of **2a**. In this case, 12 % of the diyne was also recovered intact.

Next, we examined the effect of external chloride ion (Scheme 6). Firstly, the cycloaddition of **2a** with 1-hexyne (4 equiv) was conducted in the presence of 1 mol % **1** and 5 mol % Et_4NCl at ambient temperature. As a result, the reaction reached completion within 30 min to give **9** in 87 % yield. Therefore, the added chloride ion had no impact on the ruthenium-catalyzed, partially intramolecular alkyne cyclotrimerization. Secondly, the cycloadditions of **2a** with chloroacetonitrile (**3h**) were carried out by adding 5, 10, or 20 mol % Et_4NCl with 2 mol % **1** at ambient temperature. These reactions were completed after around 20 h to give pyridine **4ah** in 68–74 % yield, along with the diyne dimer in 12–15 % yield. The chloride additive slowed the pyridine formation and facilitated somewhat the undesirable diyne dimerization, however, the amount of ammonium chloride had almost no influence on the product ratio of 82:18–86:14. The exact role of the chloride ligand is not clear at this stage, whereas the neutral ruthenium species, [Cp*RuCl], proved to have higher catalytic efficacy, and the undesired dimerization of the diyne was observed in the presence of external chloride ions. These aspects suggest that the chlorine-atom dissociation/association steps might be involved in the catalytic cycle (see below).[23]

To obtain further insight into the coordination mode of the nitriles used in this study, we performed theoretical calculations. For computational efficacy, we calculated model complexes having a Cp ligand instead of a Cp* ligand, although these two ligands afford different steric and electronic environments to the ruthenium center. Although the nitriles bearing an extra coordinating group are expected to behave as bidentate ligands, the chelate-coordination mode failed to explain the efficacy of fumalonitrile **3g**, in which the two cyanogroups are located mutually *trans* on the rigid alkene backbone. In addition, small bite angles of malononitrile **3a** or chloroacetonitrile **3h** make their chelate formation on single ruthenium species difficult. Indeed, the DFT-optimization of neutral and cationic ruthenium complexes **I** or **II** having a chelate chloroacetonitrile ligand resulted in the isomerization of oxidative-addition products **I′** or **II′** as stationary points (Figure 1). This suggests that the nitriles function as bridging rather than chelate ligands. As such a possibility, it was reported previously that *o*-cyanophenyldiphenylphosphine behaves as a bridging ligand in a dinuclear rhenium complex. In this example, the cyano group was considered to coordinate to the rhenium center through the C≡N triple bond.[24] Such a side-on coordination mode of

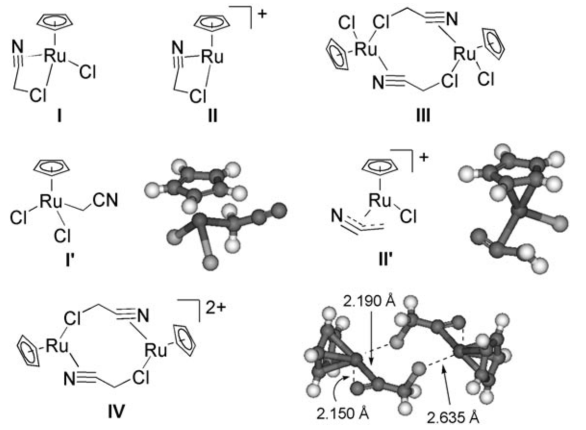
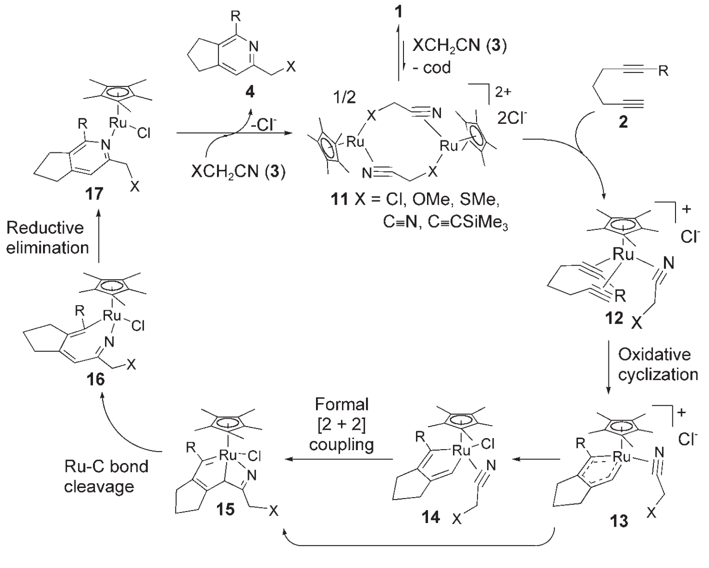


Figure 1. DFT-optimized structures of model complexes.

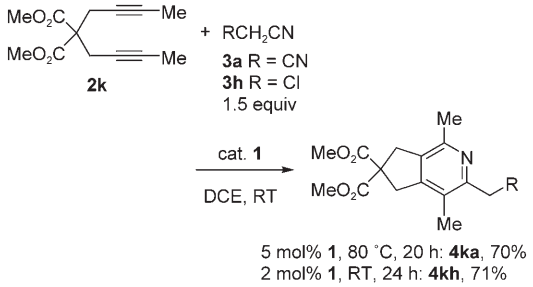
the cyano group is clearly beneficial to cyclocotrimerization leading to pyridines. Accordingly, we also assumed a symmetrical dinuclear ruthenium complex with two bridging η^2-nitrile ligands to be active species. The DFT-optimization of model complex **III** consisting of neutral [CpRuCl] fragments and chloroacetonitrile, however, led to a ring-collapsed structure. In contrast, the similar cationic complex **IV** was located successfully as a stationary point. Its Ru–C and Ru–N bond lengths of 2.190 and 2.150 Å, respectively, are similar to those reported for the isolated η^2-nitrile complexes.[19] On the other hand, the Ru–chlorine bond length of 2.635 Å is greater than the Rh–Cl distance (2.49 Å) in a related cationic pentamethylcyclopentadienylrhodium dichloromethane complex.[25] This shows that the chlorine ligand is more labile for ligand substitution than the η^2-nitrile ligand.

On the basis of these observations, a plausible catalytic cycle is outlined in Scheme 7. The initial ligand exchange from cod to nitrile **3** with concomitant chloride dissociation may give dinuclear cationic complex **11**, in which bridging side-on nitrile ligands act as six-electron donors. In other words, it might be reasonable to consider that the reacting cyano group takes the 2e-η^2-coordination mode, and an extra coordinating group (CN, Cl, F, Br, OMe, SMe, C≡CSiMe$_3$) behaves as a four-electron-donor ligand. In this respect, both ruthenium centers are coordinatively saturated 18-electron species in **11**. Substitution of labile **11** accommodates diyne **2**, resulting in the irreversible formation of mononuclear η^2-nitrile complex **12**. Subsequent oxidative cyclization of the diyne ligand leads to cationic ruthenacyclopentatriene (nitrile) complex **13**. At this stage, the chloride ion might return to the ruthenium center of **13** to afford ruthenacyclopentadiene **14** before further reaction of the coordinated nitrile. This is because the four-legged piano-stool geometry might be required for the formal [2+2] cycloaddition, leading to azaruthenatricycle **15**. The direct conversion of **13** to **15**, however, cannot be ruled out. Finally, the Ru–C bond cleavage in **15** followed by the reductive elimination of pyridine **4** from resultant **16** leads to the formation of η^1-pyridine complex **17**. The ligand exchange from **4** to nitrile **3** with concomitant chloride dissociation restores dinuclear species **11**.



Scheme 7. Plausible mechanism for ruthenium-catalyzed cycloaddition.

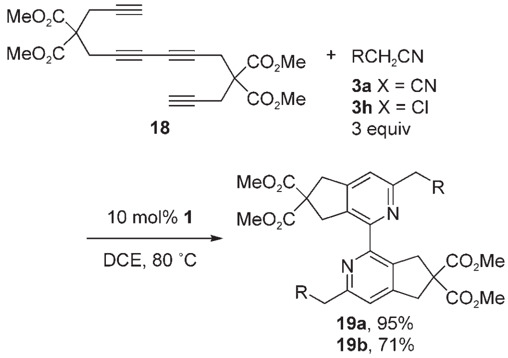
Further scope and application of ruthenium-catalyzed cyclocotrimerization: As depicted in Scheme 8, fully substituted pyridines **4ka** and **4kh** were obtained in good yields from internal diyne **2k**. Notably, the reaction of chloroacetonitrile **3h** proceeded even at ambient temperature with a lesser catalyst loading than that for malononitrile **3a**. Nitriles **3a** and **3h** were allowed to react with tetrayne **18** in refluxing DCE to afford bipyridines **19a** and **19b** in 95 and 71% yield, respectively (Scheme 9).[26]



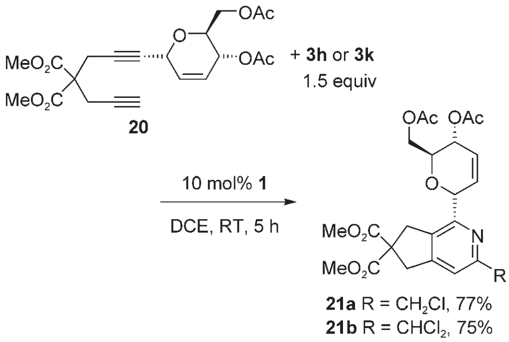
Scheme 8. Synthesis of fully substituted pyridines.

Previously, we achieved the ruthenium-catalyzed *C*-arylglycoside synthesis from *C*-diynylglycosides and monoalkynes.[12f,g] Herein, this strategy was extended to the synthesis of pyridine analogues (Scheme 10). The cycloaddition of glycoside **20** with 1.5 equivalents of **3h** or **3k** was conducted at room temperature. Although a high catalyst loading of 10 mol% was required, the desired *C*-pyridylglycosides **21a** and **21b** were synthesized selectively in good yields.

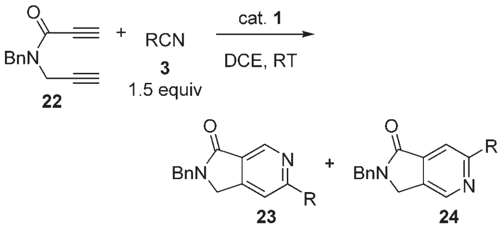
Finally, we examined the cycloaddition of diyne **22** bearing an amide tether (Scheme 11). It has been reported that such an unsymmetrical diyne reacted with terminal alkynes, electron-deficient nitriles, or isocyanates to give the corresponding cycloadducts with moderate to good regioselectivity.[8b,12d] On the basis of DFT calculations of model intermediates, the regioselectivity was ascribed to the electronic



Scheme 9. Synthesis of bipyridines.



Scheme 10. Synthesis of *C*-pyridylglycosides.



3a R = CH_2CN, 1 mol% **1**, 1 h: 90%, **23a**:**24a** = 50:50
3h R = CH_2Cl, 2 mol% **1**, 3 h: 84%, **23b**:**24b** = 50:50
3k R = $CHCl_2$, 2 mol% **1**, 3 h: 89%, **23c**:**24c** = 80:20

Scheme 11. Cycloaddition of amide-tethered diyne **22**.

influence of the internal carbonyl group. In striking contrast, no regioselectivity was observed for the cycloaddition of **22** with malononitrile (**3a**) or chloroacetonitrile (**3h**), strongly indicative that the cycloaddition of these nitriles proceeds by a different mechanism, with previous examples (see above). On the other hand, the cycloaddition of dichloroacetonitrile (**3k**) exhibited moderate regioselectivity of **23c**:**24c** = 80:20. Consequently, the cycloaddition regioselectivity depends on the number of chlorine atoms α to the cyano group, although the origin of such dependence is not clear.

Conclusion

Dicyanides and halonitriles exhibit exceptionally high reactivity toward the ruthenium-catalyzed cycloaddition with 1,6-diynes leading to bicyclic pyridines under mild conditions. Further screening of the nitrile components revealed that methoxy and methylthio groups also behave as assisting groups, whereas nitrogen functional groups, such as pyridyl and amino groups, proved to be totally ineffective. Moreover, a trimethylsilylated alkynyl group indicated a similar efficiency to the cyano group, although alkenyl and ester functionalities are incompetent. These results suggest that multiple lone pairs or π-bonds play a critical role.

Experimental Section

General: Column chromatography was performed with silica gel (Cica silica gel 60N) eluted with mixed solvents (hexane/ethyl acetate). ^1H and ^{13}C NMR spectra were measured by using a Varian Mercury 300 NMR spectrometer with $CDCl_3$ solutions at 25 °C. ^1H NMR chemical shifts are reported in terms of chemical shift (δ, ppm) relative to the singlet at 7.26 ppm for chloroform. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; sept, septet; m, multiplet. Coupling constants are reported in Hz. ^{13}C NMR spectra were fully decoupled and are reported in terms of chemical shift (δ, ppm) relative to the triplet at 77.0 ppm for $CDCl_3$. Elemental analyses were performed by the Instrumental Analysis Facility of Nagoya University or the Microanalytical Center of Kyoto University. Melting points were obtained by using a Büchi Melting Point B-540 and are uncorrected. 1,2-Dichloroethane was dried over CaH_2, distilled, and degassed before use. [Cp*RuCl(cod)] was obtained according to the literature procedures.[27]

General procedure for ruthenium-catalyzed cycloaddition: reaction of dimethyl dipropargylmalonate (2a) with malononitrile (3a): A solution of diyne **2a** (63 mg, 0.3 mmol) in dry degassed 1,2-dichloroethane (2 mL) was added to a solution of malononitrile (**3a**) (30 mg, 0.45 mmol) and [Cp*RuCl(cod)] (**1**) (2.3 mg, 0.006 mmol) in dry degassed 1,2-dichloroethane (1 mL) over 15 min by using a syringe under Ar atmosphere at RT. The reaction mixture was stirred at RT for 20 h. The solvent was evaporated and the crude product was purified by silica-gel flash column chromatography (eluent hexane/AcOEt = 2:1) to give **4aa** (76 mg, 92 %) as orange solid. Other cycloadditions were carried out in a similar way. The spectral data for **4ah** have been reported.[10]

Analytical data for cycloadducts

4aa: m.p. 81–82 °C (eluent hexane/AcOEt = 2:1); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 3.56$ (s, 2H), 3.61 (s, 2H), 3.75 (s, 6H), 3.88 (s, 2H), 7.30 (s, 1H), 8.39 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta =$ 26.5 (CH_2), 38.0 (CH_2), 40.2 (CH_2), 53.3 (CH_3), 60.1, 117.0, 118.1 (CH), 135.6, 145.4 (CH), 148.7, 151.2, 171.0 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2252$ (CN), 1732 cm^{-1} (CO_2Me); MS (FAB): *m*/*z* (%): 274 (80) [MH^+], 243 (27) [$MH^+ - OMe$], 214 (100) [$M^+ - CO_2Me$]; elemental analysis calcd (%) for $C_{14}H_{14}N_2O_4$ (274.27): C 61.31, H 5.14, N 10.21; found: C 61.41, H, 5.12, N 10.10.

4ba: oil (eluent hexane/AcOEt = 2:1); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 2.12$ (quint, $J = 7.5$ Hz, 2H), 2.92 (t, $J = 7.5$ Hz, 4H), 3.88 (s, 2H), 7.30 (s, 1H), 8.38 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 25.0$, 26.4, 30.0, 32.7, 117.3, 118.4, 139.5, 145.4, 147.6, 155.4 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2258$ cm^{-1} (CN); MS (FAB): *m*/*z* (%): 159 (100) [MH^+], 120 (19) [$MH^+ - CH_2CN$]; elemental analysis calcd (%) for $C_{10}H_{10}N_2$ (158.20): C 75.92, H 6.37, N 17.71; found: C 75.80, H, 6.50, N 17.52.

4ca: m.p. 145–146 °C (eluent hexane/AcOEt = 1:2); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 2.41$ (s, 3H), 3.90 (s, 2H), 4.63 (s, 2H), 4.65 (s, 2H), 7.29 (s, 1H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.77 (d, $J = 8.1$ Hz, 2H), 8.41 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 21.6$, 26.5, 51.5, 53.1, 116.4, 116.7, 127.3, 129.9, 132.0, 133.0, 144.0, 144.1, 147.2, 149.5 ppm; IR ($CHCl_3$): $\tilde{\nu} = 2251$ (CN), 1350 (Ts), 1165 cm^{-1} (Ts); MS (FAB): *m*/*z* (%): 314 (100) [MH^+], 158 (41) [$M^+ - Ts$]; elemental analysis calcd (%) for $C_{16}H_{15}N_3O_2S$ (313.37): C 61.32, H 4.82, N 13.41; found: C 61.26, H, 4.99, N 13.13.

4da: m.p. 80–81 °C (eluent hexane/AcOEt = 2:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 3.95 (s, 2H), 5.10 (s, 2H), 5.14 (s, 2H), 7.35 (s, 1H), 8.47 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 26.5, 71.4, 72.7, 115.0, 116.9, 134.8, 142.6, 149.0, 150.5 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2258 cm^{-1} (CN); MS (FAB): *m*/*z* (%): 161 (100) [*M*H$^+$]; elemental analysis calcd (%) for $C_9H_8N_2O$ (160.17): C 67.49, H 5.03, N 17.49; found: C 67.55, H, 4.87, N 17.48.

4ea: m.p. 121–122 °C (eluent hexane/AcOEt = 4:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 3.94 (s, 2H), 4.27 (s, 4H), 7.37 (s, 1H), 8.49 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 26.2, 35.4, 37.5, 116.8, 118.3, 136.1, 145.9, 148.4, 151.5 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2256 cm^{-1} (CN); MS (EI): *m*/*z* (%): 176 (100) [*M*$^+$], 148 (25) [*M*$^+$−2H−CN]; elemental analysis calcd (%) for $C_9H_8N_2S$ (176.24): C 61.34, H 4.58, N 15.90; found: C 61.24, H, 4.44, N 15.62.

4ab: oil (eluent hexane/AcOEt = 1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.81 (t, *J* = 7.5 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 3.58 (s, 2H), 3.60 (s, 2H), 3.76 (s, 6H), 7.08 (s, 1H), 8.38 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 16.9, 33.4, 38.1, 40.3, 53.2, 60.1, 117.0, 118.9, 119.4, 134.6, 145.1, 148.7, 150.4, 155.5, 171.2 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2247 (CN), 1732 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 289 (100) [*M*H$^+$], 229 (8) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{15}H_{16}N_2O_4$ (288.30): C 62.49, H 5.59, N 9.72; found: C 62.78, H, 5.79, N 9.22.

4ad: m.p. 125–126 °C (eluent hexane/AcOEt = 4:1–3:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 3.70 (s, 4H), 3.79 (s, 6H), 7.48 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.62 (s, 1H), 7.67 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 8.61 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 38.2, 40.4, 53.3, 60.1, 110.9, 118.6, 119.0, 128.4, 129.7, 132.6, 134.0, 135.9, 143.4, 145.4, 150.4, 153.8, 171.1 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2225 (CN), 1736 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 337 (100) [*M*H$^+$], 277 (35) [*M*$^+$−CO$_2$Me], 219 (18) [*M*$^+$−2CO$_2$Me]; elemental analysis calcd (%) for $C_{19}H_{16}N_2O_4$ (336.34): C 67.85, H 4.79, N 8.33; found: C 67.89, H, 4.66, N 8.31.

4ae: m.p. 153–154 °C (eluent hexane/AcOEt = 5:1–1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 3.66 (s, 2H), 3.67 (s, 2H), 3.78 (s, 6H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.59 (s, 1H), 7.64–7.67 (m, 1H), 8.16–8.19 (m, 1H), 8.26 (t, *J* = 1.5 Hz, 1H), 8.54 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 38.2, 40.4, 53.3, 60.2, 112.8, 116.4, 118.6, 129.4, 130.5, 130.9, 131.9, 135.8, 140.5, 145.5, 150.8, 153.7, 171.1 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2232 (CN), 1735 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 337 (100) [*M*H$^+$], 277 (10) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{19}H_{16}N_2O_4$ (336.34): C 67.85, H 4.79, N 8.33; found: C 68.08, H, 5.00, N 8.17.

4af: m.p. 178–179 °C (eluent hexane/AcOEt = 5:1–3:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 3.67 (s, 2H), 3.68 (s, 2H), 3.78 (s, 6H), 7.62 (d, *J* = 0.6 Hz, 1H), 7.67 (dt, *J* = 9.0, 2.4 Hz, 1H), 8.06 (dt, *J* = 9.0, 2.4 Hz, 1H), 8.55 ppm (d, *J* = 0.6 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 38.2, 40.4, 53.3, 60.2, 112.2, 116.9, 118.8, 127.3, 132.4, 136.0, 143.5, 145.6, 150.7, 154.0, 171.2 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2230 (CN), 1735 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 337 (100) [*M*H$^+$], 277 (10) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{19}H_{16}N_2O_4$ (336.34): C 67.85, H 4.79, N 8.33; found: C 67.65, H, 4.82, N 8.11.

4ag: m.p. 102–104 °C (eluent hexane/AcOEt = 1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 3.61 (s, 2H), 3.65 (s, 2H), 3.77 (s, 6H), 6.52 (d, *J* = 15.9 Hz, 1H), 7.19 (s, 1H), 7.35 (d, *J* = 15.9 Hz, 1H), 8.46 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 38.4, 40.2, 53.3, 60.1, 100.3, 118.0, 120.1, 138.0, 146.0, 148.6, 149.9, 150.6, 171.0 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2223 (CN), 1735 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 287 (100) [*M*H$^+$], 277 (10) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{15}H_{14}N_2O_4$ (286.28): C 62.93, H 4.93, N 9.79; found: C 62.70, H 4.89, N 9.73.

4fa: m.p. 54–55 °C (eluent hexane/AcOEt = 1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.44 (s, 3H), 3.54 (s, 2H), 3.60 (s, 2H), 3.76 (s, 6H), 3.84 (s, 2H), 7.14 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 22.0 (CH$_3$), 26.5 (CH$_2$), 38.6 (CH$_2$), 40.5 (CH$_2$), 53.3 (CH$_3$), 59.5, 115.7 (CH), 117.2, 133.6, 148.2, 150.8, 154.1, 171.2 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2256 (CN), 1736 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 288 (41) [*M*$^+$], 228 (100) [*M*$^+$−H−CO$_2$Me], 197 (28) [*M*$^+$−HOMe−CO$_2$Me]; elemental analysis calcd (%) for $C_{15}H_{16}N_2O_4$ (288.30): C 62.49, H 5.59, N 9.72; found: C 62.40, H 5.58, N 9.69.

4ga: m.p. 122–123 °C (eluent hexane/AcOEt = 1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 3.65 (s, 2H), 3.74 (s, 6H), 3.79 (s, 2H), 3.96 (s, 2H), 7.29 (s, 1H), 7.38–7.50 (m, 3H), 7.72–7.77 ppm (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 26.6, 39.9, 40.3, 53.2, 60.0, 116.6, 117.2, 128.2, 128.4, 128.8, 132.6, 138.4, 148.9, 152.5, 154.1, 171.0 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2257 (CN), 1735 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 351 (100) [*M*H$^+$], 291 (34) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{20}H_{18}N_2O_4$ (350.37): C 68.56, H 5.18, N 8.00; found: C 68.50, H 5.22, N 7.87.

4ha: m.p. 120–121 °C (eluent hexane/AcOEt = 5:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 0.33 (s, 9H), 3.56 (s, 2H), 3.63 (s, 2H), 3.77 (s, 6H), 3.89 (s, 2H), 7.20 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 1.3, 26.8, 39.4, 39.8, 53.2, 60.2, 117.1, 117.5, 140.9, 148.4, 148.5, 163.5, 171.2 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2253 (CN), 1734 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 347 (100) [*M*H$^+$], 287 (40) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{17}H_{22}N_2O_4Si$ (346.45): C 58.93, H 6.40, N 8.09; found: C 58.92, H 6.42, N 8.08.

4ia: m.p. 163–164 °C (eluent hexane/AcOEt = 1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.39 (s, 3H), 2.41 (s, 3H), 3.84 (s, 2H), 4.56 (s, 2H), 4.60 (s, 2H), 7.11 (s, 1H), 7.33 (d, *J* = 8 Hz, 2H), 7.76 ppm (d, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 21.6, 21.9, 26.5, 51.9, 53.5, 113.9, 116.9, 127.3, 129.9, 130.2, 133.2, 144.0, 146.9, 149.2, 153.2 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2256 cm^{-1} (CN); MS (FAB): *m*/*z* (%): 328 (100) [*M*H$^+$], 172 (36) [*M*$^+$−Ts]; elemental analysis calcd (%) for $C_{17}H_{17}N_3O_2S$ (327.40): C 62.36, H 5.23, N 12.83; found: C 62.19, H 5.29, N 12.53.

4ja: m.p. 127–129 °C (eluent hexane/AcOEt = 1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.42 (s, 3H), 3.89 (s, 2H), 5.07 (s, 2H), 5.09 (s, 2H), 7.17 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 22.1, 26.5, 71.8, 73.3, 112.5, 117.1, 132.9, 148.7, 150.1, 151.7 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2256 cm^{-1} (CN); MS (FAB): *m*/*z* (%): 175 (100) [*M*H$^+$]; elemental analysis calcd (%) for $C_{10}H_{10}N_2O$ (174.20): C 68.95, H 5.79, N 16.08; found: C 68.69, H 5.75, N 15.94.

4fb: m.p. 72–74 °C (eluent hexane/AcOEt = 1:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.42 (s, 3H), 2.77 (t, *J* = 7.2 Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 3.52 (s, 2H), 3.56 (s, 2H), 3.75 (s, 6H), 6.90 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 17.2, 22.0, 33.4, 38.5, 40.5, 53.2, 59.4, 116.5, 119.4, 132.6, 149.9, 153.6, 155.2, 171.4 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2250 (CN), 1734 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 303 (100) [*M*H$^+$], 243 (34) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{16}H_{18}N_2O_4$ (302.33): C 63.56, H 6.00, N 9.27; found: C 63.73, H 6.06, N 9.18.

4fc: m.p. 78–79 °C (eluent hexane/AcOEt = 1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.07 (q, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 2.84 (t, *J* = 7.2 Hz, 2H), 3.53 (s, 2H), 3.57 (s, 2H), 3.76 (s, 6H), 6.87 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 16.7, 22.1, 25.5, 36.6, 38.6, 40.6, 53.2, 59.4, 116.5, 119.6, 132.0, 149.9, 153.4, 157.5, 171.5 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2249 (CN), 1734 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 317 (100) [*M*H$^+$], 257 (44) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{17}H_{20}N_2O_4$ (316.35): C 64.54, H 6.37, N 8.86; found: C 64.70, H 6.44, N 8.61.

4fd: m.p. 131–132 °C (eluent hexane/AcOEt = 3:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.57 (s, 3H), 3.63 (s, 2H), 3.69 (s, 2H), 3.79 (s, 6H), 7.42 (s, 1H), 7.46 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.75 (t, *J* = 1.2 Hz, 1H), 7.78 ppm (t, *J* = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 22.1, 38.7, 40.7, 53.3, 59.5, 109.1, 111.1, 116.7, 118.7, 128.3, 129.7, 132.6, 134.0, 143.7, 150.1, 153.5, 154.1, 171.4 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2227 (CN), 1738 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 351 (100) [*M*H$^+$], 289 (11) [*M*$^+$−2H−CO$_2$Me]; elemental analysis calcd (%) for $C_{20}H_{18}N_2O_4$ (350.37): C 68.56, H 5.18, N 8.00; found: C 68.50, H 5.32, N 7.75.

4fg: m.p. 119–121 °C (eluent hexane/AcOEt = 5:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 2.47 (s, 3H), 3.57 (s, 2H), 3.61 (s, 2H), 3.77 (s, 6H), 6.53 (d, *J* = 15.9 Hz, 1H), 7.02 (s, 1H), 7.32 ppm (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 22.3, 38.9, 40.4, 53.3, 59.4, 99.8, 118.1, 118.1, 136.4, 148.8, 149.5, 150.0, 154.7, 171.2 ppm; IR (CHCl$_3$): $\tilde{\nu}$ = 2221 (CN), 1735 cm^{-1} (CO$_2$Me); MS (FAB): *m*/*z* (%): 301 (100) [*M*H$^+$], 241 (12) [*M*$^+$−CO$_2$Me]; elemental analysis calcd (%) for $C_{16}H_{16}N_2O_4$ (300.31): C 63.99, H 5.37, N 9.33; found: C 63.86, H 5.30, N 9.34.

4ai: oil (eluent hexane/AcOEt = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.62 (s, 4H), 3.76 (s, 6H), 5.45 (d, J = 46.8 Hz, 2H), 7.33 (s, 1H), 8.40 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.0, 40.3, 53.1, 60.0, 84.4 (d, J = 167.9 Hz), 116.5 (d, J = 5.6 Hz), 135.4 (d, J = 0.5 Hz), 144.6 (d, J = 1.1 Hz), 150.4, 154.6 (d, J = 21.1 Hz), 171.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1737 cm^{-1} (CO_2Me); MS (EI): m/z (%): 267 (43) [M^+], 236 (10) [M^+−OMe], 207 (100) [M^+−H−CO_2Me], 176 (22) [M^+−H−CO_2Me−OMe]; elemental analysis calcd (%) for $C_{13}H_{14}FNO_4$ (267.25): C 58.42, H 5.28, N 5.24; found: C 58.38, H 5.25, N 5.14.

4aj: oil (eluent hexane/AcOEt = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.65 (s, 4H), 3.78 (s, 6H), 4.62 (s, 2H), 7.41 (s, 1H), 8.42 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 33.9, 38.0, 40.2, 53.2, 60.0, 119.3, 135.6, 145.0, 150.7, 155.0, 171.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1736 cm^{-1} (CO_2Me); MS (EI): m/z (%): 327 (13) [M^+], 267 (35) [M^+−H−CO_2Me], 248 (34) [M^+−Br], 188 (100) [M^+−H−CO_2Me−Br]; elemental analysis calcd (%) for $C_{13}H_{14}BrNO_4$ (328.16): C 47.58, H 4.30, N 4.27; found: C 47.69, H 4.44, N 4.02.

4ak: oil (eluent hexane/AcOEt = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.65 (s, 4H), 3.77 (s, 6H), 6.72 (s, 1H), 7.63 (s, 1H), 8.38 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.1, 40.3, 53.3, 60.0, 71.5, 116.9, 137.2, 144.1, 151.3, 156.4, 170.9 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1737 cm^{-1} (CO_2Me); MS (EI): m/z (%): 317 (27) [M^+], 282 (13) [M^+−Cl], 257 (85) [M^+−H−CO_2Me], 222 (100) [M^+−H−CO_2Me−Cl]; elemental analysis calcd (%) for $C_{13}H_{13}Cl_2NO_4$ (318.15): C 49.08, H 4.12, N 4.40; found: C 49.11, H 3.94, N 4.27.

4bh: oil (eluent hexane/AcOEt = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.12 (quint, J = 7.8 Hz, 2H), 2.93 (t, J = 7.8 Hz, 4H), 4.65 (s, 2H), 7.34 (s, 1H), 8.41 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.0, 30.0, 32.6, 47.1, 119.0, 139.6, 145.0, 153.8, 154.8; MS (EI): m/z (%): 167 (100) [M^+]; elemental analysis calcd (%) for C_8H_8ClNO (167.64): C 64.48, H 6.01, N 8.36; found: C 64.68, H 5.90, N 8.14.

4ch: m.p. 155.2–156.1 °C (eluent hexane/AcOEt = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.41 (s, 3H), 4.64 (s, 4H), 4.65 (s, 2H), 7.31–7.35 (m, 2H), 7.33 (s, 1H), 7.75–7.78 (m, 2H), 8.41 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.6, 45.4, 51.6, 53.2, 116.9, 127.3, 129.8, 131.9, 133.1, 143.6, 144.0, 146.7, 155.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1349 (NTs), 1162 cm^{-1} (NTs); MS (EI): m/z (%): 322 (21) [M^+], 167 (100) [M^+−Ts]; elemental analysis calcd (%) for $C_{15}H_{15}ClN_2O_2S$ (322.81): C 55.81, H 4.68, N 8.68; found: C 56.00, H 4.59, N 8.58.

4dh: oil (eluent hexane/AcOEt = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.71 (s, 2H), 5.11 (s, 2H), 5.15 (s, 2H), 7.40 (s, 1H), 8.49 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 46.6, 71.5, 72.8, 115.5, 134.7, 142.1, 150.0, 155.3; MS (EI): m/z (%): 169 (100) [M^+], 141 (91) [M^+−CO]; elemental analysis calcd (%) for C_8H_8ClNO (169.61): C 56.65, H 4.75, N 8.26; found: C 56.89, H 4.70, N 8.07.

4eh: m.p. 85.0–86.0 °C (eluent hexane/AcOEt = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.27 (brs, 4H), 4.68 (s, 2H), 7.39 (s, 1H), 8.49 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 35.5, 37.6, 46.4, 118.9, 136.1, 145.5, 151.1, 154.7; MS (EI): m/z (%): 185 (35) [M^+], 149 (100) [M^+−Cl]; elemental analysis calcd (%) for C_8H_8ClNS (185.67): C 51.75, H 4.34, N 7.54; found: C 51.66, H 4.22, N 7.20.

4al: oil (eluent hexane/AcOEt = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.85 (d, J = 6.9 Hz, 3H), 3.61 (s, 2H), 3.62 (s, 2H), 3.76 (s, 6H), 5.12 (q, J = 6.9 Hz, 1H), 7.35 (s, 1H), 8.39 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.2, 38.1, 40.4, 53.3, 59.1, 60.1, 117.0, 135.5, 144.6, 150.6, 159.3, 171.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1737 cm^{-1} (CO_2Me); MS (EI): m/z (%): 297 (6) [M^+], 262 (100) [M^+−Cl], 238 (12) [M^+−CO_2Me], 202 (66) [M^+−H−CO_2Me−Cl]; elemental analysis calcd (%) for $C_{14}H_{16}ClNO_4$ (297.73): C 56.48, H 5.42, N 4.70; found: C 56.65, H 5.34, N 4.61.

4am: oil (eluent hexane/AcOEt = 10:1–6:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.61 (s, 2H), 3.64 (s, 2H), 3.73 (dd, J = 13.8, 7.2 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.94 (dd, J = 13.8, 6.0 Hz, 1H), 4.27 (brs, 1H), 4.59 (dd, J = 7.2, 6.0 Hz, 1H), 6.65 (d, J = 8.1 Hz, 2H), 6.73 (t, J = 8.1 Hz, 1H), 7.17 (t, J = 8.1 Hz, 2H), 7.36 (s, 1H), 8.43 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.1, 40.3, 49.9, 53.3, 60.0, 60.9, 113.1, 117.9, 118.7, 129.2, 135.9, 144.9, 146.7, 150.6, 156.2, 171.0, 171.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1736 cm^{-1} (CO_2Me); MS (EI): m/z (%): 388 (2) [M^+], 352 (100) [M^+−HCl], 236 (21) [M^+−H−CO_2Me−NHPh]; elemental analysis calcd (%) for $C_{20}H_{21}ClN_2O_4$ (388.84): C 61.78, H 5.44, N 7.20; found: C 61.73, H 5.39, N 6.93.

4an: oil (eluent hexane/AcOEt = 8:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.63 (s, 2H), 3.64 (s, 2H), 3.77 (s, 6H), 5.68 (s, 1H), 6.46 (s, 1H), 7.63 (s, 1H), 8.43 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.1, 40.3, 53.2, 60.1, 115.6, 116.76, 136.0, 138.1, 144.5, 150.5, 151.9, 171.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1737 cm^{-1} (CO_2Me); MS (EI): m/z (%): 295 (48) [M^+], 260 (10) [M^+−Cl], 235 (88) [M^+−H−CO_2Me], 200 (100) [M^+−H−CO_2Me−Cl]; elemental analysis calcd (%) for $C_{14}H_{14}ClNO_4$ (295.06): C 56.86, H 4.77, N 4.74; found: C 56.89, H 4.71, N 4.61.

4ao: oil (eluent hexane/AcOEt = 8:1–3:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.70–1.77 (m, 4H), 2.35–2.40 (m, 2H), 2.78–2.84 (m, 2H), 3.64 (s, 2H), 3.65 (s, 2H), 3.77 (s, 6H), 7.86 (s, 1H), 8.39 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 17.1, 24.9, 38.1, 40.4, 46.1, 53.3, 60.0, 91.1, 117.5, 119.2, 136.4, 143.7, 151.0, 157.9, 171.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 2251 (CN), 1737 cm^{-1} (CO_2Me); MS (EI): m/z (%): 399 (1) [MH$^+$], 363 (35) [M^+−Cl], 316 (100) [M^+−$(CH_2)_4$CN]; elemental analysis calcd (%) for $C_{18}H_{20}Cl_2N_2O_4$ (399.27): C 54.15, H 5.05, N 7.02; found: C 54.40, H 4.95, N 6.87.

4ap: oil (eluent hexane/AcOEt = 20:1–10:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.41–1.62 (m, 4H), 2.02–2.11 (m, 2H), 2.73–2.79 (m, 2H), 3.65 (s, 4H), 3.77 (s, 6H), 4.91–5.03 (m, 2H), 5.72–5.85 (m, 1H), 7.84 (s, 1H), 8.41 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.1, 28.3, 33.5, 38.0, 40.4, 47.2, 53.2, 60.0, 92.1, 114.5, 117.3, 136.1, 138.3, 143.8, 150.7, 158.3, 171.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1737 cm^{-1} (CO_2Me); MS (EI): m/z (%): 399 (5) [M^+], 364 (52) [M^+−Cl], 316 (100) [M^+−H−$(CH_2)_4CH{=}CH_2$]; elemental analysis calcd (%) for $C_{19}H_{23}Cl_2NO_4$ (400.30): C 57.01, H 5.79, N 3.50; found: C 57.09, H 5.80, N 3.40.

4aq: oil (eluent hexane/AcOEt = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.53–1.72 (m, 4H), 1.94 (t, J = 2.4 Hz, 1H), 2.21 (dt, J = 7.2, 2.4 Hz, 2H), 2.75–2.80 (m, 2H), 3.65 (s, 2H), 3.66 (s, 2H), 3.78 (s, 6H), 7.85 (s, 1H), 8.41 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.3, 24.9, 27.9, 38.1, 40.4, 46.7, 53.3, 60.0, 68.5, 84.0, 91.9, 117.3, 136.2, 143.8, 150.8, 158.2, 171.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3305 (C≡CH), 1737 cm^{-1} (CO_2Me); MS (EI): m/z (%): 398 (8) [MH$^+$], 362 (35) [M^+−Cl], 316 (100) [M^+−$(CH_2)_4$C°CH]; elemental analysis calcd (%) for $C_{19}H_{21}Cl_2NO_4$ (398.28): C 57.30, H 5.31, N 3.52; found: C 57.16, H 5.03, N 3.33.

4as: oil (eluent hexane/AcOEt = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.47 (s, 3H), 3.60 (s, 2H), 3.61 (s, 2H), 3.76 (s, 6H), 4.55 (s, 2H), 7.30 (s, 1H), 8.40 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 38.1, 40.4, 53.2, 58.8, 60.1, 75.4, 117.2, 134.7, 144.5, 150.3, 156.7, 171.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1735 cm^{-1} (CO_2Me); MS (EI): m/z (%): 279 (2) [M^+], 249 (100) [MH$^+$−OMe], 220 (9) [M^+−CO_2Me]; elemental analysis calcd (%) for $C_{14}H_{17}NO_5$ (279.29): C 60.21, H 6.14, N 5.02; found: C 60.48, H 6.10, N 4.79.

4at: oil (eluent hexane/AcOEt = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.06 (s, 3H), 3.59 (s, 4H), 3.76 (s, 8H), 7.24 (s, 1H), 8.36 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.3, 38.1, 40.0, 40.3, 53.2, 58.8, 60.1, 118.7, 134.3, 144.6, 150.3, 157.0, 171.3 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1734 cm^{-1} (CO_2Me); MS (EI): m/z (%): 295 (1) [M^+], 249 (100) [MH$^+$−SMe]; elemental analysis calcd (%) for $C_{14}H_{17}NO_4S$ (295.35): C 56.93, H 5.80, N 4.74; found: C 57.15, H 5.80, N 4.60.

4fh: m.p. 79.6–81.4 °C (eluent hexane/AcOEt = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.47 (s, 3H), 3.56 (s, 2H), 3.61 (s, 2H), 3.77 (s, 6H), 4.61 (s, 2H), 7.18 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.9, 38.5, 40.5, 46.9, 53.2, 59.4, 116.4, 133.6, 150.2, 153.4, 154.5, 171.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1736 cm^{-1} (CO_2Me); MS (EI): m/z (%): 297 (34) [M^+], 266 (6) [M^+−OMe], 237 (100) [M^+−H−CO_2Me], 202 (19) [M^+−H−CO_2Me−Cl]; elemental analysis calcd (%) for $C_{14}H_{16}ClNO_4$ (297.73): C 56.48, H 5.42, N 4.70; found: C 56.69, H 5.35, N 4.56.

4gh: oil (eluent hexane/AcOEt = 10:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.66 (s, 2H), 3.75 (s, 6H), 3.78 (s, 2H), 4.72 (s, 2H), 7.36 (s, 1H), 7.38–7.51 (m, 3H), 7.72–7.77 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 39.9, 40.3, 46.9, 53.2, 60.0, 117.2, 128.2, 128.3, 128.5, 132.6, 138.7, 151.9, 153.5, 155.2, 171.1 ppm; IR ($CHCl_3$): $\tilde{\nu}=1736\ \mathrm{cm^{-1}}$ (CO_2Me); MS (EI): m/z (%): 359 (44) [M^+], 328 (4) [$M^+-\mathrm{OMe}$], 300 (100) [$M^+-\mathrm{CO_2Me}$], 264 (32) [$M^+-\mathrm{H}-\mathrm{CO_2Me}-\mathrm{Cl}$]; elemental analysis calcd (%) for $C_{19}H_{18}ClNO_4$ (359.80): C 63.42, H 5.04, N 3.89; found: C 63.77, H 4.92, N 3.66.

4hh: m.p. 87.0–88.0 °C (eluent hexane/AcOEt = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.34$ (s, 9H), 3.56 (s, 2H), 3.63 (s, 2H), 3.76 (s, 6H), 4.67 (s, 2H), 7.27 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=-1.3$, 39.5, 39.8, 47.5, 53.2, 60.2, 117.7, 140.9, 148.0, 154.7, 162.3, 171.3 ppm; IR ($CHCl_3$): $\tilde{\nu}=1736$ (CO_2Me), 1259 cm^{-1} (TMS); MS (EI): m/z (%): 355 (32) [M^+], 340 (54) [$M^+-\mathrm{Me}$], 296 (100) [$M^+-\mathrm{CO_2Me}$]; elemental analysis calcd (%) for $C_{16}H_{22}ClNO_4Si$ (355.89): C 54.00, H 6.23, N 3.94; found: C 54.09, H 6.42, N 3.69.

4ih: m.p. 143.0–144.0 °C (eluent hexane/AcOEt = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.42$ (s, 3H), 4.57–4.59 (m, 2H), 4.59 (s, 2H), 4.61–4.63 (m, 2H), 7.15 (s, 1H), 7.32–7.35 (m, 2H), 7.75–7.79 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=21.5$, 21.9, 46.6, 52.0, 53.6, 114.5, 127.3, 129.8, 130.1, 133.2, 143.9, 146.4, 152.5, 155.5 ppm; IR ($CHCl_3$): $\tilde{\nu}=1345$ (NTs), 1164 cm^{-1} (NTs); MS (EI): m/z (%): 336 (10) [M^+], 181 (100) [$M^+-\mathrm{Ts}$]; elemental analysis calcd (%) for $C_{16}H_{17}ClN_2O_2S$ (336.84): C 57.05, H 5.09, N 8.32; found: C 56.84, H 5.32, N 8.07.

4jh: m.p. 81.0–82.0 °C (eluent hexane/AcOEt = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.46$ (s, 3H), 4.66 (s, 2H), 5.08–5.13 (m, 4H), 7.22 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=22.1$, 46.7, 71.9, 73.3, 113.1, 132.9, 149.6, 151.0, 155.0; MS (EI): m/z (%): 183 (90) [M^+], 155 (100) [$M^+-\mathrm{CO}$], 119 (65) [$M^+-\mathrm{CO}-\mathrm{Cl}$]; elemental analysis calcd (%) for $C_9H_{10}ClNO$ (183.63): C 58.86, H 5.49, N 7.63; found: C 59.08, H 5.65, N 7.25.

4fr: oil (eluent hexane/AcOEt = 6:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.54$ (s, 3H), 3.63 (s, 2H), 3.68 (s, 2H), 3.79 (s, 6H), 7.29 (s, 1H), 7.28–7.35 (m, 2H), 7.42–7.46 (m, 1H), 7.50–7.73 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=22.2$, 38.7, 40.6, 53.2, 59.4, 118.2, 126.7, 129.1, 129.8, 131.3, 131.9, 132.9, 139.3, 149.0, 153.4, 155.0, 171.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=1734\ \mathrm{cm^{-1}}$ (CO_2Me); MS (EI): m/z (%): 359 (83) [M^+], 299 (100) [$M^+-\mathrm{H}-\mathrm{CO_2Me}$], 239 (45) [$M^+-2\,\mathrm{H}-2\,\mathrm{CO_2Me}$]; elemental analysis calcd (%) for $C_{19}H_{18}ClNO_4$ (359.80): C 63.42, H 5.04, N 3.89; found: C 63.64, H 5.07, N 3.65.

4fs: oil (eluent hexane/AcOEt = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.46$ (s, 3H), 3.46 (s, 3H), 3.55 (s, 2H), 3.60 (s, 2H), 3.76 (s, 6H), 4.51 (s, 2H), 7.13 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=21.9$, 38.6, 40.6, 53.1, 58.7, 59.5, 75.5, 114.8, 132.7, 149.8, 153.0, 156.3, 171.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=1734\ \mathrm{cm^{-1}}$ (CO_2Me); MS (EI): m/z (%): 293 (1) [M^+], 263 (100) [$M\mathrm{H}^+-\mathrm{OMe}$], 203 (15) [$M^+-\mathrm{CO_2Me}$]; elemental analysis calcd (%) for $C_{15}H_{19}NO_5$ (293.32): C 61.42, H 6.53, N 4.78; found: C 61.43, H 6.52, N 4.38.

4ft: oil (eluent hexane/AcOEt = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.07$ (s, 3H), 2.45 (s, 3H), 3.54 (s, 2H), 3.59 (s, 2H), 3.74 (s, 2H), 3.77 (s, 6H), 7.07 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=15.3$, 22.0, 38.5, 39.9, 40.5, 53.1, 59.4, 116.2, 132.3, 149.8, 153.0, 156.4, 171.3 ppm; IR ($CHCl_3$): $\tilde{\nu}=1734\ \mathrm{cm^{-1}}$ (CO_2Me); MS (EI): m/z (%): 309 (1) [M^+], 263 (100) [$M\mathrm{H}^+-\mathrm{SMe}$], 202 (15) [$M^+-\mathrm{HSMe}-\mathrm{CO_2Me}$]; elemental analysis calcd (%) for $C_{15}H_{19}NO_4S$ (309.38): C 58.23, H 6.19, N 4.53; found: C 58.34, H 6.22, N 4.43.

4au: oil (eluent hexane/AcOEt = 10:1–6:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.20$ (s, 9H), 3.60 (s, 2H), 3.61 (s, 2H), 3.76 (s, 6H), 3.80 (s, 2H), 7.40 (s, 1H), 8.34 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=0.2$, 29.1, 38.0, 40.4, 53.2, 60.1, 87.8, 102.9, 117.7, 134.0, 144.6, 150.4, 154.8, 171.3 ppm; IR ($CHCl_3$): $\tilde{\nu}=2176$ ($C\equiv C$), 1734 (CO_2Me), 1277 (TMS), 846 cm^{-1} (TMS); MS (EI): m/z (%): 344 (100) [$M^+-\mathrm{H}$], 273 (35) [$M^+-\mathrm{H}-\mathrm{SiMe_3}$]; elemental analysis calcd (%) for $C_{18}H_{23}NO_4Si$ (345.47): C 62.58, H 6.71, N 4.05; found: C 62.53, H 6.54, N 3.81.

4fu: oil (eluent hexane/AcOEt = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.19$ (s, 9H), 2.43 (s, 3H), 3.54 (s, 2H), 3.61 (s, 2H), 3.77 (s, 8H), 7.24 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=0.1$, 21.9, 29.1, 38.5, 40.6, 53.1, 59.4, 87.7, 103.1, 115.3, 132.0, 150.0, 152.9, 154.4, 171.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=2176$ ($C\equiv C$), 1734 (CO_2Me), 1271 (TMS), 846 cm^{-1} (TMS); MS (EI): m/z (%): 359 (28) [M^+], 344 (100) [$M^+-\mathrm{Me}$], 287 (25) [$M^+-\mathrm{H}-\mathrm{SiMe_3}$]; elemental analysis calcd (%) for $C_{19}H_{25}NO_4Si$ (359.49): C 63.48, H 7.01, N 3.90; found: C 63.28, H 6.96, N 3.50.

4fv: oil (eluent hexane/AcOEt = 6:1–5:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=0.17$ (s, 9H), 2.55 (s, 3H), 3.62 (s, 2H), 3.65 (s, 2H), 3.78 (s, 8H), 7.30 (dd, $J=7.5$, 1.5 Hz, 1H), 7.39 (dt, $J=7.5$, 1.5 Hz, 1H), 7.56 (dd, $J=7.5$, 1.5 Hz, 1H), 7.67 (s, 1H), 7.71 ppm (dd, $J=7.5$, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=-0.1$, 22.2, 38.6, 40.6, 53.1, 59.6, 97.6, 104.6, 117.8, 120.8, 127.5, 128.7, 129.5, 132.7, 133.4, 142.5, 148.5, 153.3, 155.5, 171.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=2153$ ($C\equiv C$), 1737 (CO_2Me), 1272 (TMS), 855 cm^{-1} (TMS); MS (EI): m/z (%): 421 (14) [M^+], 406 (8) [$M^+-\mathrm{Me}$], 348 (100) [$M^+-\mathrm{SiMe_3}$], 288 (28) [$M^+-\mathrm{SiMe_3}-\mathrm{H}-\mathrm{CO_2Me}$], 229 (56) [$M^+-\mathrm{SiMe_3}-\mathrm{H}-2\,\mathrm{CO_2Me}$]; elemental analysis calcd (%) for $C_{24}H_{27}NO_4Si$ (421.56): C 68.38, H 6.46, N 3.32; found: C 68.60, H 6.41, N 3.15.

4ka: m.p. 115–117 °C (eluent hexane/AcOEt = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.24$ (s, 3H), 2.40 (s, 3H), 3.55 (s, 4H), 3.76 (s, 6H), 3.80 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=14.8$, 21.6, 24.7, 39.0, 39.8, 53.3, 59.3, 116.8, 124.9, 133.9, 146.3, 149.5, 151.0, 171.3 ppm; IR ($CHCl_3$): $\tilde{\nu}=2251$ (CN), 1734 cm^{-1} (CO_2Me); MS (FAB): m/z (%): 303 (100) [$M\mathrm{H}^+$], 243 (34) [$M^+-\mathrm{CO_2Me}$]; elemental analysis calcd (%) for $C_{16}H_{18}N_2O_4$ (302.33): C 63.56, H 6.00, N 9.27; found: C 63.41, H 6.11, N 9.46.

4kh: m.p. 99.0–100.2 °C (eluent hexane/AcOEt = 8:1–2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.31$ (s, 3H), 2.43 (s, 3H), 3.56 (s, 2H), 3.57 (s, 2H), 3.78 (s, 6H), 4.67 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=14.4$, 21.6, 39.1, 39.8, 45.5, 53.2, 59.3, 125.9, 134.1, 149.4, 150.4, 152.2, 171.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=1736\ \mathrm{cm^{-1}}$ (CO_2Me); MS (EI): m/z (%): 311 (55) [M^+], 276 (14) [$M^+-\mathrm{Cl}$], 251 (100) [$M^+-\mathrm{H}-\mathrm{CO_2Me}$], 216 (89) [$M^+-\mathrm{H}-\mathrm{CO_2Me}-\mathrm{Cl}$]; elemental analysis calcd (%) for $C_{15}H_{18}ClNO_4$ (311.76): C 57.79, H 5.82, N 4.49; found: C 57.99, H 5.77, N 4.33.

19a: m.p. 188–189 °C (eluent hexane/AcOEt = 5:1–1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=3.64$ (s, 4H), 3.76 (s, 12H), 3.96 (s, 4H), 4.10 (s, 4H), 7.28 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=26.5$, 40.2, 41.3, 53.2, 59.7, 116.9, 117.7, 135.7, 147.8, 151.8, 153.3, 171.5 ppm; IR ($CHCl_3$): $\tilde{\nu}=2253$ (CN), 1734 cm^{-1} (CO_2Me); MS (FAB): m/z (%): 547 (100) [$M\mathrm{H}^+$], 487 (13) [$M^+-\mathrm{CO_2Me}$]; elemental analysis calcd (%) for $C_{28}H_{26}N_4O_8$ (546.53): C 61.53, H 4.80, N 10.25; found: C 61.75, H 4.93, N 10.12.

19b: m.p. 185.9–186.3 °C (eluent hexane/AcOEt = 4:1–3:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=3.65$ (s, 4H), 3.76 (s, 12H), 4.07 (s, 4H), 4.71 (s, 4H), 7.36 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=40.2$, 41.1, 46.8, 53.1, 59.7, 118.0, 135.4, 151.5, 152.5, 154.0, 171.6 ppm; IR ($CHCl_3$): $\tilde{\nu}=1733\ \mathrm{cm^{-1}}$ (CO_2Me); MS (EI): m/z (%): 564 (18) [M^+], 505 (100) [$M^+-\mathrm{CO_2Me}$]; elemental analysis calcd (%) for $C_{26}H_{26}Cl_2N_2O_8$ (565.40): C 55.23, H 4.64, N 4.95; found: C 55.61, H 4.58, N 4.62.

21a: oil (eluent hexane/AcOEt = 3:1–2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.09$ (s, 3H), 2.11 (s, 3H), 3.55 (d, $J=18.0$ Hz, 1H), 3.62 (d, $J=18.0$ Hz, 1H), 3.73 (d, $J=18.0$ Hz, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 3.83 (d, $J=18.0$ Hz, 1H), 4.17–4.22 (m, 2H), 4.30 (dd, $J=12.6$, 7.8 Hz, 1H), 4.62 (s, 2H), 5.16–5.20 (m, 1H), 5.40 (dd, $J=4.5$, 2.7 Hz, 1H), 6.02 (ddd, $J=10.5$, 3.9, 2.1 Hz, 1H), 6.23 (ddd, $J=10.5$, 2.7, 1.2 Hz, 1H), 7.32 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=20.8$, 21.0, 38.4, 40.0, 46.6, 53.1, 53.2, 59.8, 62.2, 64.3, 71.4, 73.6, 118.3, 122.8, 130.9, 134.3, 152.1, 153.3, 154.3, 170.3, 170.6, 171.2 ppm; IR ($CHCl_3$): $\tilde{\nu}=1738\ \mathrm{cm^{-1}}$ (CO_2Me); MS (EI): m/z (%): 495 (14) [M^+], 436 (37) [M^+-$\mathrm{CO_2Me}$], 376 (40) [$M^+-\mathrm{H}-2\,\mathrm{CO_2Me}$], 334 (100) [$M^+-\mathrm{H}-2\,\mathrm{CO_2Me}-\mathrm{H_2C{=}C{=}O}$]; elemental analysis calcd (%) for $C_{23}H_{26}ClNO_9$ (495.91): C 55.71, H 5.28, N 2.82; found: C 55.92, H 5.15, N 2.75.

21b: oil (eluent hexane/AcOEt = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=2.09$ (s, 3H), 2.11 (s, 3H), 3.60 (d, $J=18.0$ Hz, 1H), 3.67 (d, $J=18.0$ Hz, 1H), 3.75 (d, $J=18.0$ Hz, 1H), 3.76 (s, 3H), 3.77 (s, 3H), 3.85 (d, $J=18.0$ Hz, 1H), 4.14–4.33 (m, 3H), 5.16–5.22 (m, 1H), 5.40 (dd, $J=4.5$, 2.4 Hz, 1H), 6.02 (ddd, $J=10.5$, 3.9, 2.1 Hz, 1H), 6.22 (ddd, $J=10.5$, 2.4, 0.9 Hz, 1H), 6.68 (s, 1H), 7.62 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=20.8$, 21.0, 38.5, 40.0, 53.1, 53.2, 59.8, 62.2, 64.3, 71.4, 73.4, 116.6, 123.2, 130.5, 136.0, 152.6, 152.8, 155.9, 170.2, 170.5, 171.0, 171.1 ppm; IR (CHCl$_3$): $\tilde{\nu}=1739\,\mathrm{cm^{-1}}$ (CO$_2$Me); MS (EI): m/z (%): 529 (25) $[M^+]$, 470 (45) $[M^+-\mathrm{CO_2Me}]$, 428 (63) $[M^+-\mathrm{CO_2Me}-\mathrm{H_2C{=}C{=}O}]$, 410 (64) $[M^+-\mathrm{H}-2\,\mathrm{CO_2Me}]$, 368 (100) $[M^+-\mathrm{H}-2\,\mathrm{CO_2Me}-\mathrm{H_2C{=}C{=}O}]$; elemental analysis calcd (%) for $\mathrm{C_{23}H_{25}Cl_2NO_9}$ (530.35): C 52.09, H 4.75, N 2.64; found: C 52.38, H 4.65, N 2.45.

23a/24a: m.p. 135.2–138.2 °C (eluent hexane/AcOEt = 1:1–1:3); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): **23a**: $\delta=4.06$ (s, 2H), 4.33 (s, 2H), 4.80 (s, 2H), 7.28–7.39 (m, 5H), 7.56 (s, 1H), 9.06 ppm (s, 1H); **24a**: $\delta=4.08$ (s, 2H), 4.38 (s, 2H), 4.83 (s, 2H), 7.28–7.39 (m, 5H), 7.90 (s, 1H), 8.73 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): **23a**: $\delta=26.9$, 46.4, 49.1, 116.6, 127.9, 128.0, 128.1, 128.2, 128.8, 136.0, 145.8, 151.3, 152.5, 165.7 ppm; **24a**: $\delta=26.7$, 46.7, 48.0, 116.5, 127.9, 128.1, 128.8, 135.2, 135.8, 141.8, 144.8, 150.2, 165.6 ppm; IR (CHCl$_3$): $\tilde{\nu}=2259$ (CN), $1697\,\mathrm{cm^{-1}}$ (CONBn); MS (FAB): m/z (%): 263 (100) $[M^+]$, 236 (4) $[M^+-\mathrm{HCN}]$, 186 (12) $[M^+-\mathrm{C_6H_5}]$, 159 (37) $[M^+-\mathrm{HCN}-\mathrm{C_6H_5}]$; elemental analysis calcd (%) for $\mathrm{C_{16}H_{13}N_3O}$ (263.29): C 72.99, H 4.98, N 15.96; found: C 72.90, H 5.01, N 16.01.

23b/24b: m.p. 99.9–101.8 °C (eluent hexane/AcOEt = 2:1–1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): **23b**: $\delta=4.32$ (s, 2H), 4.77 (s, 2H), 4.80 (s, 2H), 7.28–7.39 (m, 5H), 7.58 (s, 1H), 9.07 ppm (s, 1H); **24b**: $\delta=4.37$ (s, 2H), 4.78 (s, 2H), 4.83 (s, 2H), 7.28–7.39 (m, 5H), 7.96 (s, 1H), 8.71 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): **23b**: $\delta=46.3$, 46.4, 49.1, 117.0, 127.8, 127.9, 128.0, 128.7, 136.0, 145.2, 150.8, 158.5, 165.9 ppm; **24b**: $\delta=46.4$, 46.6, 47.9, 116.8, 127.7, 128.0, 128.7, 135.0, 135.9, 141.4, 144.2, 156.4, 165.9 ppm; IR (CHCl$_3$): $\tilde{\nu}=1695\,\mathrm{cm^{-1}}$ (CONBn); MS (FAB): m/z (%): 272 (100) $[M^+]$, 237 (8) $[M^+-\mathrm{Cl}]$, 195 (12) $[M^+-\mathrm{C_6H_5}]$, 168 (38) $[M\mathrm{H}^+-\mathrm{NBn}]$; elemental analysis calcd (%) for $\mathrm{C_{15}H_{13}ClN_2O}$ (272.73): C 66.06, H 4.80, N 10.27; found: C 66.25, H 4.78, N 10.10.

23c/24c: oil (eluent hexane/AcOEt = 3:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): **23c**: $\delta=4.36$ (s, 2H), 4.81 (s, 2H), 6.82 (s, 1H), 7.28–7.39 (m, 5H), 7.87 (s, 1H), 9.03 ppm (s, 1H); **24c**: $\delta=4.39$ (s, 2H), 4.83 (s, 2H), 6.83 (s, 1H), 7.28–7.39 (m, 5H), 8.25 (s, 1H), 8.69 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): **23c**: $\delta=46.4$, 49.2, 71.0, 115.8, 127.9, 128.0, 128.1, 128.8, 135.9, 144.7, 151.3, 159.6, 165.5 ppm; **24c**: $\delta=46.7$, 48.0, 71.0, 115.5, 127.9, 128.0, 129.2, 135.8, 136.4, 142.0, 143.7, 157.7, 165.4 ppm; IR (CHCl$_3$): $\tilde{\nu}=1696\,\mathrm{cm^{-1}}$ (CONBn); MS (FAB): m/z (%): 306 (100) $[M^+]$, 271 (28) $[M^+-\mathrm{Cl}]$, 236 (43) $[M^+-2\,\mathrm{Cl}]$; elemental analysis calcd (%) for $\mathrm{C_{15}H_{12}Cl_2N_2O}$ (307.17): C 58.65, H 3.94, N 9.12; found: C 58.69, H 3.78, N 8.91.

General procedure for synthesis of cyanodiynes: A solution of 5-oxa-octa-2,7-diyne-1-ol (993 mg, 8.0 mmol) in dry DMF (5 mL) was added to a solution of NaH (60% in oil, 480 mg, 12.0 mmol) in dry DMF (10 mL) at 0 °C and stirred for 1 h at RT. A solution of bromoacetonitrile (1.15 g, 9.6 mmol) in dry DMF (5 mL) was added at 0 °C and the resulting solution was stirred overnight at RT. The reaction mixture was poured onto ice water (20 mL) and extracted with ether (3×10 mL). The combined organic layer was dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica-gel-column flash chromatography (eluent, hexane/AcOEt = 7:1) to afford **7a** (110 mg, 34%) as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta=2.47$ (t, $J=2.7$ Hz, 1H), 4.26 (d, $J=2.7$ Hz, 2H), 4.33 (t, $J=1.5$ Hz, 2H), 4.37 (s, 2H), 4.38 ppm (t, $J=1.5$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta=54.1$, 56.5, 56.6, 58.2, 75.2, 78.5, 80.1, 84.0, 115.3 ppm; IR (CHCl$_3$): $\tilde{\nu}=3305$ ($\mathrm{C{\equiv}CH}$), $2122\,\mathrm{cm^{-1}}$ ($\mathrm{C{\equiv}N}$); MS (EI): m/z (%): 163 (13) $[M^+]$, 121 (100) $[M^+-\mathrm{CH_2C{\equiv}CH}]$; elemental analysis calcd (%) for $\mathrm{C_9H_9NO_2}$ (163.17): C 66.25, H 5.56, N 8.58; found: C 66.01, H 5.79, N 8.31.

In a similar manner, **7b** was prepared from 8-bromo-4-oxaocta-1,6-diyne and dimethyl cyanomethylmalonate (86% yield). Oil (eluent, hexane/AcOEt = 3:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta=2.46$ (t, $J=2.4$ Hz, 1H), 3.08 (t, $J=2.1$ Hz, 2H), 3.14 (s, 2H), 3.82 (s, 6H), 4.21 (d, $J=2.4$ Hz, 2H), 4.23 ppm (t, $J=2.1$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta=21.9$, 23.9, 53.7, 54.8, 56.2, 56.5, 75.1, 78.6, 79.8, 115.7, 167.4 ppm; IR (CHCl$_3$): $\tilde{\nu}=3303$ ($\mathrm{C{\equiv}CH}$), 2257 ($\mathrm{C{\equiv}N}$), $1745\,\mathrm{cm^{-1}}$ (CO$_2$Me); MS (EI): m/z (%): 278 (6) $[M\mathrm{H}^+]$, 218 (100) $[M^+-\mathrm{CO_2Me}]$; elemental analysis calcd (%) for $\mathrm{C_{14}H_{15}NO_5}$ (277.27): C 60.64, H 5.45, N 5.05; found: C 60.93, H 5.50, N 4.71.

In a similar manner, **7c** was prepared from 6-cyano-5-oxahexa-2-yne-1-ol and bromo-2-butyne (66% yield). Oil (eluent, hexane/AcOEt = 8:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta=1.85$ (t, $J=2.1$ Hz, 3H), 4.18 (q, $J=2.1$ Hz, 2H), 4.27 (t, $J=1.5$ Hz, 2H), 4.35 (t, $J=1.5$ Hz, 2H), 4.36 ppm (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta=3.7$, 54.1, 56.3, 57.3, 58.3, 73.9, 79.7, 83.4, 84.4, 115.3 ppm; IR (CHCl$_3$): $\tilde{\nu}=2242\,\mathrm{cm^{-1}}$ ($\mathrm{C{\equiv}N}$); MS (EI): m/z (%): 176 (14) $[M^+-\mathrm{H}]$, 148 (100) $[M^+-\mathrm{H}-\mathrm{HC{\equiv}N}]$; elemental analysis calcd (%) for $\mathrm{C_{10}H_{11}NO_2}$ (177.08): C 67.78, H 6.26, N 7.90; found: C 67.73, H 6.25, N 7.49.

General procedure for ruthenium-catalyzed cyclization of cyanodiynes: A solution of **7a** (49.0 mg, 0.30 mmol) in DCE (20 mL) was added to a solution of [Cp*RuCl(cod)] (11.6 mg, 0.031 mmol) in dry degassed DCE (10 mL) over 3 h through a syringe pump at RT. The reaction mixture was stirred for further 24 h and then concentrated in vacuo. The residue was purified by silica-gel-column flash chromatography (eluent, hexane/AcOEt = 1:1) to afford **8a** (34.1 mg, 70%) as pale-yellow solid. M.p. 98.3–99.1 °C; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta=5.03$ (brs, 2H), 5.09 (brs, 2H), 5.12 (brs, 2H), 5.17 (brs, 2H), 8.41 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta=71.0$, 71.6, 71.7, 72.7, 125.4, 134.0, 141.7, 142.4, 159.6 ppm; MS (EI): m/z (%): 163 (100) $[M^+]$, 135 (41) $[M^+-\mathrm{CO}]$, 106 (60) $[M^+-\mathrm{H}-2\,\mathrm{CO}]$; elemental analysis calcd (%) for $\mathrm{C_9H_9NO_2}$ (163.17): C 66.25, H 5.56, N 8.58; found: C 66.08, H 5.70, N 8.37.

Analytical data for 8b: m.p. 105.1–106.2 °C (eluent hexane/AcOEt = 3:1); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta=3.53$ (s, 2H), 3.70 (s, 2H), 3.77 (s, 6H), 5.03 (brs, 2H), 5.12 (brs, 2H), 8.31 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta=37.0$, 41.5, 53.3, 58.1, 71.7, 71.9, 126.4, 133.8, 141.2, 144.8, 159.8, 171.4 ppm; IR (CHCl$_3$): $\tilde{\nu}=1736\,\mathrm{cm^{-1}}$ (CO$_2$Me); MS (EI): m/z (%): 277 (83) $[M^+]$, 246 (13) $[M^+-\mathrm{OMe}]$, 217 (100) $[M^+-\mathrm{H}-\mathrm{CO_2Me}]$; elemental analysis calcd (%) for $\mathrm{C_{14}H_{15}NO_5}$ (277.27): C 60.64, H 5.45, N 5.05; found: C 60.45, H 5.79, N 4.90.

Analytical data for 8c: m.p. 123.1–124.2 °C (eluent hexane/AcOEt = 1:1–1:2); ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): $\delta=2.46$ (s, 3H), 5.05 (brs, 4H), 5.09 (brs, 2H), 5.11 ppm (brs, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): $\delta=22.0$, 71.1, 72.2, 72.7, 122.8, 131.8, 142.0, 150.7, 159.4 ppm; MS (EI): m/z (%): 177 (100) $[M^+]$, 148 (38) $[M^+-\mathrm{H}-\mathrm{CO}]$, 120 (44) $[M^+-\mathrm{H}-2\,\mathrm{CO}]$; elemental analysis calcd (%) for $\mathrm{C_{10}H_{11}NO_2}$ (177.08): C 67.78, H 6.26, N 7.90; found: C 67.73, H 6.25, N 7.50.

Computational methods: The Gaussian 03 program package was used for all geometry optimizations.[27] The geometries of model complexes **I–IV** were fully optimized by means of the Becke's three-parameter hybrid density functional method (B3LYP)[28] with the basis set, consisting of a double-ζ basis set with the relativistic effective core potential of Hay and Wadt (LanL2 ECP)[29] for Ru, and the 6–31G(d)[30] basis sets for other elements.

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