Chemo- and regioselective crossed alkyne cyclotrimerisation of 1,6-diynes with terminal monoalkynes mediated by Grubbs' catalyst or Wilkinson's catalyst†

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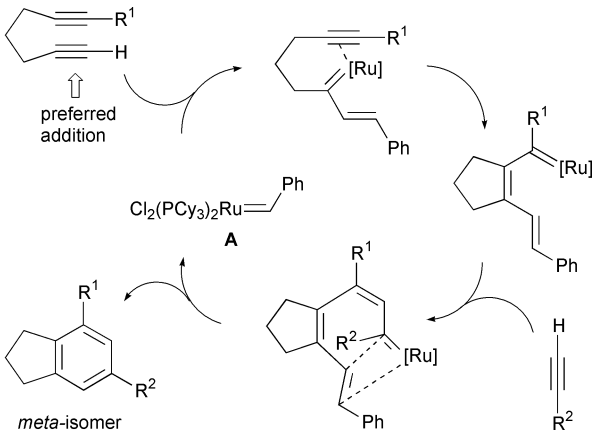
A novel protocol for crossed alkyne cyclotrimerisations mediated by Grubbs' catalyst [$RuCl_2$(=CHPh)(PCy_3)$_2$] allows the efficient synthesis of 4,6-substituted indolines with high regioselectivity, and it is complementary to alkyne cyclotrimerisations mediated by Wilkinson's catalyst [RhCl(PPh_3)$_3$] allowing the regioselective synthesis of the corresponding 4,5-substituted isomers in many cases.

The transition metal catalysed cyclotrimerisation of alkynes has been recognised as a versatile synthetic approach for highly substituted benzenes.[1] While the intramolecular version has been established as an efficient synthetic method, the efficiency of the conceptually more flexible crossed cyclotrimerisation of tethered diynes with monoalkynes has to be evaluated by the ability to gain control over the chemo- and regioselectivity of this process.[2] Only a few reports appear using differently substituted diynes and monoalkynes in crossed cyclotrimerisation reactions,[2d,h,m,3] and in most cases the observed regioselectivity was either dependent on a reactivity preference of a given substrate or limited by the use of sterically encumbered substituents.

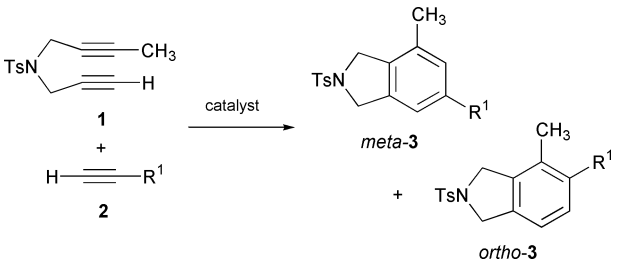
Recently, we reported a novel synthesis of indolines based on a rhodium-catalysed crossed cyclotrimerisation with *N*-functionalised alk-1-ynylamides, a process which provides flexible access to 4-, or 7-, as well as to 4- and 7-substituted indolines.[3] While servicing a number of objectives in indole synthesis, this method has not yet been applicable for the regioselective synthesis of indolines bearing substituents in the 4,6-, or 4,5-position—a feature of numerous compounds of synthetic and medicinal interest.[4] We propose below a solution to this challenging issue by using either Grubbs' catalyst [$RuCl_2$(=CHPh)(PCy_3)$_2$] **A** or Wilkinson's catalyst [RhCl(PPh_3)$_3$] **B** in crossed alkyne cyclotrimerisations.

At the outset of our studies we anticipated that a crossed alkyne cyclotrimerisation based on a cascade of metathesis steps could contribute to the above problem set, because metathesis catalytic cycles usually begin with a regioselective addition of the ylidene-transition metal complex to the less hindered site of an olefinic or acetylenic substrate.[5] Based on the findings of Blechert and Roy, that the complex **A** caused a fully intra- or intermolecular alkyne cyclotrimerisation,[6] we projected a catalytic cycle as outlined in Scheme 1. The preferred addition of complex **A** to the least substituted alkyne moiety of the 1,6-diyne should be supported by a coordination of the remaining triple bond to the ruthenium complex, thus causing the chemo- and regioselectivity of this process. A cascade of intra- and intermolecular, as well as ring closing metathesis steps, which are related to the well established enyne and olefin metathesis,[7] would finally result in the liberation of the ruthenium benzylidene catalyst and in the preferred formation of the corresponding *meta*-isomer.

A first set of examples was obtained by the reaction of the 1,6-diyne **1** (0.02 M in CH_2Cl_2) with the monoalkynes **2a–d** (5 eq.) in the presence of 5 mol% **A** at 40 °C (Scheme 2, Table 1). During a period of 10–20 h the starting material was consumed giving the isoindolines **3a–d** in 81–89% yield after chromatography on silica gel (entries 1–4). Although in some cases the amount of **2** could be reduced to 2 eq., best results were obtained using 5 eq., which effectively suppressed a competitive cotrimerisation of **1**. In agreement with our mechanistic hypoth-



Scheme 1



Scheme 2

Table 1 Cycloaddition of **1** with **2a–d** mediated by Grubbs'catalyst **A** or Wilkinson's catalyst **B**‡[a]

Entry	**2**	R^1	Catalyst (mol%)	Yield (%)[b]		*meta*:*ortho*[c]
1	**2a**	Ph	**A** (5)	**3a**	82	5:1
2	**2b**	C_3H_7	**A** (5)	**3b**	92	6:1
3	**2c**	CH_2OH	**A** (5)	**3c**	81	6:1
4	**2d**	$(CH_2)_2OH$	**A** (5)	**3d**	89	6:1
5	**2a**	Ph	**B** (5)	**3a**	52	1:8
6	**2b**	C_3H_7	**B** (5)	**3b**	61	1:4
7	**2c**	CH_2OH	**B** (5)	**3c**	90	1:10
8	**2d**	$(CH_2)_2OH$	**B** (5)	**3d**	79	1:1.5

[a] *Reaction conditions:* monoalkyne (5 eq.), reactions with catalyst **A** [$RuCl_2$(=CHPh)(PCy_3)$_2$] were run in CH_2Cl_2 at 40 °C in a sealed tube for various reaction times (10–20 h), reactions with catalyst **B** [RhCl(PPh_3)$_3$] were run in toluene at rt for various reaction times (10–15 h). [b] Yield after purification by silica gel chromatography. [c] Determined by ^{1}H-NMR.

† Electronic supplementary information (ESI) available: experimental procedures and analytical data for **3**, **4** and **5**. See http://www.rsc.org/suppdata/cc/b0/b005636g/

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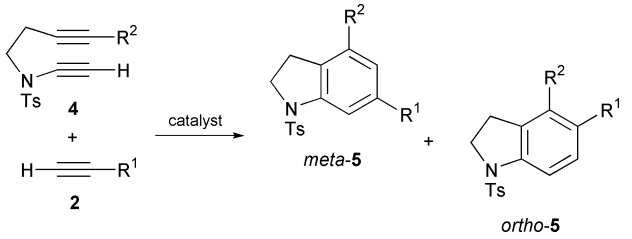

Scheme 3

Table 2 Cycloaddition of **4a**–**b** with **2b**–**e** mediated by Grubbs' catalyst **A** or Wilkinson's catalyst **B**‡[a]

Entry	4	R^2	2	R^1	Catalyst (mol%)	Yield (%)[b]	*meta*:*ortho*[c]
1	**4a**	CH_3	**2c**	CH_2OH	**A** (5)	**5a** 70	9:1
2	**4a**	CH_3	**2d**	$(CH_2)_2OH$	**A** (10)	**5b** 51	9:1
3	**4a**	CH_3	**2e**	$(CH_2)_3OH$	**A** (10)	**5c** 57	9:1
4	**4b**	Ph	**2c**	CH_2OH	**A** (10)	**5d** 60	9.5:1
5	**4a**	CH_3	**2b**	C_3H_7	**B** (5)	**5e** 54	1:10
6	**4a**	CH_3	**2c**	CH_2OH	**B** (5)	**5a** 67	1:20
7	**4a**	CH_3	**2d**	$(CH_2)_2OH$	**B** (5)	**5b** 66	1:3
8[d]	**4b**	Ph	**2c**	CH_2OH	**B** (5)	**5f** 70	1:1

[a] *Reaction conditions:* monoalkyne (5 eq.), reactions with catalyst **A** [$RuCl_2$(=CHPh)(PCy_3)$_2$] were run in CH_2Cl_2 at 40 °C in a sealed tube for various times (10–20 h), reactions with catalyst **B** [$RhCl(PPh_3)_3$] were run in toluene at rt for various reaction times (10–15 h). [b] Yield after purification by silica gel chromatography. [c] Determined by ^{1}H-NMR. [d] Reaction run at 100 °C.

esis, well pronounced selectivities were observed with ratios of *meta*:*ortho* = 5:1 and 6:1 for **3a** and **3b**–**d**, respectively.‡

Most strikingly, when the same set of compounds was treated with 5 mol% Wilkinson's catalyst **B** in toluene at 20 °C, the regioselectivities of the above reactions could be reversed giving the *ortho*-isomers of **3a**–**d** as major products with ratios of *meta*:*ortho* = 1:8, 1:4, 1:10, and 1:1.5, respectively (Table 1, entries 5–8).§ However, in the case of complex **B**—a catalyst that is assumed to operate through rhodacyclooligoolefins as intermediates in alkyne cyclotrimerisations—the outcome of regioselectivity was markedly dependent on the substituent of the monoalkyne **2**.

Finally, we applied our findings to the regioselective synthesis of 4,6- and 4,5-substituted indolines using either complex **A** or **B** as catalyst and the 1,6-diynes **4a** (R^2 = Me) or **4b** (R^2 = Ph) together with the monoalkynes **2b**–**e** (Scheme 3, Table 2).[8] When complex **A** was applied in CH_2Cl_2 at 40 °C the indolines **5a**–**d** were obtained in 51–70% yield, and once again with excellent *meta*-selectivities of *meta*:*ortho* = 9:1 and 9.5:1 for **5a**–**c** and **5d**, respectively (entries 1–4). However, a higher catalyst load of 10 mol% **A** was in some cases necessary for the completion of the reaction. Notably, nearly uniform isomer ratios were observed being independent of the substitution pattern of the alkynes used. These uniform ratios and comparably higher selectivities for the formation of the 4,6-substituted indolines *meta*-**5a**–**d** should be attributed to the electron richness of the alk-1-ynylamide moiety in **4a** and **4b** causing a clear and distinct preference for the addition of the electrophilic ruthenium benzylidene complex **A** to this electron rich triple bond and thus underlying our mechanistic hypothesis.

Gratifyingly, when the 1,6-diyne **4a** and the monoalkynes **2b**,**c** were treated with 5 mol% Wilkinson's catalyst **B** in toluene at 20 °C, again a switch in regioselectivity was observed, allowing the regioselective synthesis of 4,5-substituted indolines.§ Under these conditions the products **5e** and **5b** were obtained in 54 and 67% yield with excellent selectivities of *meta*:*ortho* = 1:10, and 1:20, respectively (entries 5 and 6). However, only a moderate preference for the *ortho*-isomer of **5b** (*meta*:*ortho* = 1:3) was found in the reaction of **4a** (R^2 = CH_3) with but-3-yn-1-ol **2d**, and the reaction of **4b** (R^2 = Ph) with **2c** occurred without a significant selectivity. Obviously crossed alkyne cyclotrimerisation catalysed by complex **B** are more sensitive to steric hindrance and the substitution pattern of the alkynes, than those catalysed by **A**.

In conclusion, we have achieved a new protocol for chemo- and regioselective crossed alkyne cyclotrimerisations mediated by Grubbs' complex **A**, which is most likely based on a cascade of metathesis steps. This novel catalytic protocol offers an efficient, flexible and highly regioselective access to 4,6-substituted indolines. Moreover, in many cases the regioselectivity of the alkyne cyclotrimerisation could be switched affording the corresponding 4,5-substituted indolines, when Wilkinson's catalyst **B** was used. Notably, both catalysts are commercially available and tolerate a wide range of functionalities.

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Notes and references

‡ All new compounds exhibited satisfactory spectra and elemental analyses. The regioisomers could be separated by simple flash chromatography on silica gel.

§ Regioselectivities of crossed alkyne cyclotrimerisations using catalyst **B** were solvent dependent. Best selectivities were obtained with non-polar solvents like toluene. A detailed discussion on the solvent-dependency of this process will be presented in the full account of this study.

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