## Highly chemo- and regio-selective [2 + 2 + 2] cycloaddition of unsymmetrical 1,6-diynes with terminal alkynes catalyzed by Cp\*Ru(cod)Cl under mild conditions<sup>†</sup>

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## Ru(II)-catalyzed cycloaddition of unsymmetrical 1,6-diynes gives the desired cycloadducts in high yields with a regioselectivity *meta*: ortho = 88:12-98:2.

Transition-metal catalyzed [2 + 2 + 2] cyclotrimerizations of alkynes has been recognized as a straightforward route to substituted benzenes.1 The control of both the chemo- and regio-chemistries in the cyclotrimerization of two or three different alkyne components, however, have been a crucial problem. Although the selective cyclocotrimerization of three different alkynes was achieved using stoichiometric zirconocene reagent,2 the regiochemistry problem has remained unsolved. In addition, catalytic reactions are ideal from both the environmental and economical points of view. The intramolecular cyclization of triynes was pioneered as a completely chemo- and regio-selective process by Vollhardt in work on the catalytic reactions of  $CpCo(CO)_2$ ,<sup>3</sup> and subsequently, many trivne cyclizations have been applied for the syntheses of complex polycyclic systems.<sup>4</sup> Intermolecular couplings between a divne and a monoalkyne have also been realized as a successful method to construct bicyclic frameworks.<sup>3,5</sup> At the expense of the complete regio- and chemo-selections, this partially intermolecular approach becomes more advantageous than the triyne methodology, because a wide variety of readily accessible or commercially available divnes and monoalkynes could directly be used. The chemoselectivity can be improved using an excess amount of a monoalkyne, although a satisfactory level of regiocontrol has not been achieved in previous diyne-monoalkyne couplings. Herein, we report the first Rucatalyzed regioselective cycloaddition between unsymmetrical 1,6-divnes and monoalkynes.

Recently, we have found that Cp\*Ru(cod)Cl 1: (Cp\* = pentamethylcyclopentadienyl, cod = cycloocta-1,5-diene) effectively catalyzes the selective intermolecular coupling of 1,6-heptadiynes with 2,5-dihydrofuran.<sup>6</sup> In order to extend the catalytic utility of the ruthenium complex 1, we further explored the catalyzed cross-cyclotrimerization of 1,6-diynes with monoalkynes. To the best of our knowledge, ruthenium-catalyzed [2 + 2 + 2] cyclotrimerizations of monoalkynes has scarcely been investigated so far,<sup>7</sup> and no example of co-cyclotrimerization of different alkynes was found in previous reports.<sup>1,8</sup> At the outset, dimethyl dipropargylmalonate **2a** [X = C(CO<sub>2</sub>Me)<sub>2</sub>] and 2 equiv. of hex-1-yne **3a** (R = Bu) were treated with 1 mol% of 1 in 1,2-dichloroethane at *ambient* temperature (Scheme 1). The



† Electronic supplementary information (ESI) available: experimental procedures and analytical data for **4** and **6**. See http://www.rsc.org/suppdata/cc/b0/b000466i/

starting divne 2a was completely consumed within 15 min, and silica-gel column chromatography of the crude reaction mixture gave the desired indan derivative 4a in 89% yield (TOF = 356)  $h^{-1}$ ; Table 1, entry 1). The undesired competitive dimerization and trimerization of 2a were effectively suppressed (11%), and the cyclotrimerization of 3a was not detected in the crude reaction mixture by <sup>1</sup>H NMR spectroscopy. The yield and the selectivity were slightly improved using 4 equiv. of **3a** (entry 2). The reaction of phenyl acetylene **3b** ( $\mathbf{R} = \mathbf{Ph}$ ) required a longer reaction time (14 h) even using 3 mol% of 1a (entry 3). A biphenyl derivative 4b was obtained in 74% yield. In contrast to these results, a terminal alkyne possessing a bulky substituent, *tert*-butyl acetylene 3c (R = Bu<sup>t</sup>) gave the corresponding cycloadduct 4c only in low yield (entry 4). In this case, substantial amounts of the dimer and the trimer of 2a were formed. In addition to terminal alkynes, the parent acetylene 3d (R = H) was found to be an effective monoalkyne component for our catalyzed cycloaddition. The diyne 2a was treated with 1 at 0 °C for 1 h under acetylene gas (balloon) to afford 4d in 84% yield (entry 5).

Table 1 Cp\*Ru(cod)Cl-catalyzed cycloaddition of 1,6-diynes  $2a{-}c$  with terminal alkynes  $3^{\alpha}$ 

Entry	X	R	Catalyst (mol%)	t	Yield <sup>b</sup> (%)	
					4	Dimer + trimer
1	C(CO <sub>2</sub> Me) <sub>2</sub>	Bu	1	15 min	<b>4a</b> , 89	11
2	$C(CO_2Me)_2$	$Bu^c$	1	15 min	<b>4a</b> , 94	5
3	$C(CO_2Me)_2$	Ph	3	14 h	<b>4b</b> , 74	21
4	$C(CO_2Me)_2$	But	1	30 min	4c, 21	53
5	$C(CO_2Me)_2$	$\mathbf{H}^{d}$	1	1 h	4d, 84	9
6	NTs	Bu	1	10 min	<b>4e</b> , 80	
7	0	Bu	1	12 h	<b>4f</b> , 68	18

<sup>*a*</sup> All reactions were carried out with a terminal alkyne (2 equiv.) in 1,2-dichloroethane at r.t. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> 4 equiv. <sup>*d*</sup> Under acetylene gas (balloon) at 0 °C.

Furthermore, this novel protocol using the Ru(II)-catalyst was successfully applied to other heterocyclic species. The cycloaddition of *N*,*N*-dipropargyl tosylamide **2b** (X = NTs) with hex-1-yne **3a** was complete within 10 min at ambient temperature to afford an isoindoline derivative **4e** as the sole product in 80% yield (entry 6). A phthalan derivative **4f** was obtained in 68% yield along with the dimer and trimer of **2c** (entry 7).

We next investigated the regiochemistry in the cycloaddition of a series of unsymmetrical 1,6-diynes **5** (Scheme 2). The regiochemistry of the cyclotrimerization key steps have been examined only to a limited degree: a few examples of regioselective cycloaddition using ClRh(PPh<sub>3</sub>)<sub>3</sub> have been reported, but these were limited to alkynes possessing a hydroxyl group.<sup>5*f*,*k*</sup> In fact, the reaction of a malonate derivative **5a** [X = C(CO<sub>2</sub>Me)<sub>2</sub>, R<sup>1</sup> = Me] with hexyne **3a** at 60 °C for 3 days using 5 mol% ClRh(PPh<sub>3</sub>)<sub>3</sub> gave a 5,7-disubstituted indan derivative *meta*-**6a** and its 5,6-disubstituted isomer *ortho*-**6a** in



Table 2 Cp\*Ru(cod)Cl-catalyzed cycloaddition of 1,6-diynes 5a-c with terminal alkynes  $3^{a}$ 

	X	$\mathbb{R}^1$	R <sup>2</sup>	Catalyst (mol%)	Yield <sup><math>b</math></sup> (%)	
Entry					t	$(meta:ortho)^{c}$
1	$C(CO_2Me)_2$	Me	Bu	1	1 h	<b>6a</b> , 85 (93:7)
2	$C(CO_2Me)_2$	Me	$Me^d$	3	18 h	<b>6b</b> , 80 (94:6)
3	$C(CO_2Me)_2$	Me	CH <sub>2</sub> OMe	1	3 h	<b>6c</b> , 86 (94:6)
4	$C(CO_2Me)_2$	Me	Ph	3	24 h	<b>6d</b> , 82 (88:12)
5	$C(CO_2Me)_2$	Ph	Bu	10	24 h	<b>6e</b> , 80 (95:5)
6	$C(CO_2Me)_2$	SiMe <sub>3</sub>	Bu	5	7 h	<b>6f</b> , 94 (98:2)
7	NTs	Me	Bu	1	10 min	6g, 82 (93:7)
8	0	Me	Bu	1	30 min	<b>6h</b> , 75 (95:5)

<sup>*a*</sup> All reactions were carried out with a terminal alkyne (2 equiv.) in 1,2-dichloroethane at r.t. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Ratios in parentheses were determined by GC analyses of isolated products. <sup>*d*</sup> Under propyne gas (balloon).

61% total yield with a low regioselectivity meta: ortho = 65:35. In our hands, 5a regioselectively reacted with 2 equiv. of 3a in the presence of the catalyst 1 (1 mol%) to afford *meta*-6a and ortho-6a in 85% total yield with an excellent regioselectivity meta: ortho = 93:7 (Table 2, entry 1). The importance of the bulky Cp\* ligand of 1 was clearly demonstrated by the fact that the reaction of 5a and 3a conducted using CpRu(cod)Cl bearing a smaller Cp ligand gave cycloadduct 6a in 76% yield with lower selectivity (meta: ortho = 87:13). Similarly, the reaction of **5a** with propyne gas **3e** ( $\mathbb{R}^2$ = H; balloon) or propargyl methyl ether **3f** ( $\hat{R}^2 = CH_2OMe$ ) gave 6b and 6c in 80 and 86% yields, respectively with high meta-selectivities (entries 2 and 3). The ether functionality at the propargylic position in 3f did not decrease both the yield and regioselectivity. Cycloaddition with the less reactive aromatic alkyne, phenylacetylene 3b, was conducted using an increased amount of the catalyst, and biphenyl derivatives 6d were obtained in a comparable total yield (82%) with somewhat lower selectivity (entry 4). Similar biphenyl derivatives 6e were also obtained from the reaction of a 1,6-diyne possessing a phenyl group as a terminal substituent **5b** (entry 5). In this case, the increased amount of the catalyst (10 mol%) was again found to be effective. The highest yield and regioselectivity were achieved in the reaction of a diyne 5c having a bulky trimethylsilyl substituent at the terminal position with 3a (entry 6). The corresponding indan derivatives 6f were obtained in 94% total yield with an isomer ratio of *meta*: ortho = 98:2. The regioselective syntheses of highly substituted heterocycles were also realized using nitrogen- or oxygen-tethered unsymmetrical divnes 5d and 5e. An isoindoline derivative 6g and a phthalan derivative **6h** were obtained in 82 and 75% yields, respectively, with high *meta*-selectivities (entries 7 and 8).

The origin of the high *meta*-selectivity can be explained by the insertion mechanism depicted in Scheme 3. A ruthenacyclopentadiene 7 formed from 1 and 5 can be proposed as a key intermediate.<sup>9</sup> In order to avoid the steric interaction with the terminal substituent  $R^1$ , a monoalkyne 3 is selectively inserted into the less substituted Ru–C single bond to form ruthenacycloheptatriene intermediates 8 or 9. At this stage, the bulky Cp\*



ligand directs formation of **8** because the steric repulsion between  $Cp^*$  and  $R^2$  is obviously greater in **9** and reductive elimination from **8** gives a *meta*-isomer *meta*-**6** as the major product.

In conclusion, an Ru(II) complex possessing a bulky planar ligand, Cp\*Ru(cod)Cl, catalyzed the cycloaddition of 1,6-diynes with terminal alkynes at or below room temperature. Satisfactory chemoselectivity can be achieved using 2 equiv. of a monoalkyne. Excellent *meta*-selectivity was observed for the reaction of unsymmetrical diynes.

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