CHEMCOMM Communication
www.rsc.org/chemcomm

Ruthenium(II)-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes with electron-deficient nitriles†

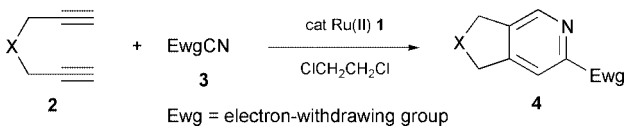
Yoshihiko Yamamoto, Satoshi Okuda and Kenji Itoh*

Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan. E-mail: Itohk@apchem.nagoya-u.ac.jp

Received (in Cambridge, UK) 20th March 2001, Accepted 3rd May 2001
First published as an Advance Article on the web 25th May 2001

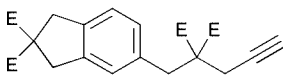
Ru(II)-catalyzed cycloaddition of 1,6-diynes with electron-deficient nitriles gave the desired bicyclic pyridines in moderate to high yields.

Transition-metal-catalyzed [2 + 2 + 2] cyclocotrimerization of two alkyne molecules and a nitrile has been recognized as a straightforward protocol providing substituted pyridines.[1,2] Although the selective cyclocotrimerization of two different alkynes and a nitrile was achieved using stoichiometric cobalt[1] or zirconium reagents,[3] the catalytic controls of both the chemo- and regiochemistries have remained as a crucial problem. In this context, the intermolecular coupling between an α,ω-diyne and a nitrile was first pioneered by Vollhardt *et al*. in their work on the catalytic reactions of $CpCo(CO)_2$,[4,5] and subsequently this strategy has been successfully applied for the synthesis of Vitamin B_6.[6] Electron-deficient nitriles, however, have been reported to be hardly involved in such a useful pyridine annulation. Ethyl cyanoformate and pentafluorobenzonitrile gave the desired pyridines only in poor yields, lower than 10%. In sharp contrast, we found that a ruthenium(II) complex, Cp*Ru(cod)Cl (Cp* = pentamethylcyclopentadienyl **1**), effectively catalyses the cycloaddition of 1,6-diynes and nitriles activated by an electron-withdrawing group (Scheme 1), although the same Ru(II) complex failed to promote the reaction with simple nitriles such as acetonitrile or benzonitrile.[7]



Scheme 1

Typically, to a solution of dimethyl dipropargylmalonate (**2a**)‡ in 1,2-dichloroethane was added a solution of the catalyst **1** and ethyl cyanoformate (**3a**) (0.02 and 1.5 equiv. to **2a**, respectively) in 1,2-dichloroethane at rt. The solution was stirred for 30 min at 60 °C to give the desired pyridine **4a** in 83% yield (Table 1, entry 1). The side reaction of **2a** leading to arene byproducts was completely suppressed. In the same manner, benzoyl cyanide (**3b**) gave the corresponding pyridine **4b** as a sole product in high yield (entry 2). On the other hand, acetyl cyanide (**3c**) and tosyl cyanide (**3d**) required higher catalyst loading (10 mol%) and temperature (80 °C). The former selectively gave the desired pyridine **4c** in 90% yield (entry 3), although the concomitant formation of the dimer **5a** was observed in the reaction of **3d** (entry 4). In addition to acyl and sulfonyl cyanides, polyhaloalkylcyanides could be used for the



5a E = CO_2Me

† Electronic supplementary information (ESI) available: experimental procedures and analytical data for compounds **4**, **7** and **8**. See http://www.rsc.org/suppdata/cc/b1/b102588k/

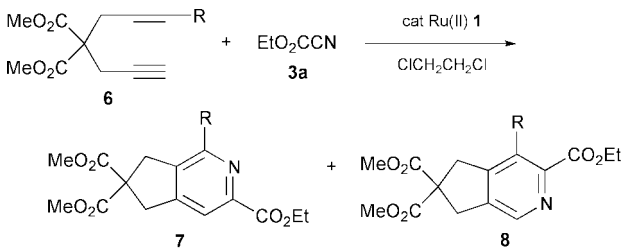
Table 1 Cp*Ru(cod)Cl-catalyzed cycloaddition of 1,6-diynes **2a–c** with electron-deficient nitriles **3a–f**[a]

Entry	X	Ewg	Catalyst/ mol %	*T*/°C	*t*/h	Yield[b]
1	$C(CO_2Me)_2$	CO_2Et	2	60	0.5	**4a**, 83%
2	$C(CO_2Me)_2$	COPh	2	60	0.5	**4b**, 84%
3	$C(CO_2Me)_2$	COMe	10	80	1	**4c**, 90%
4	$C(CO_2Me)_2$	Ts	10	80	24	**4d**, 31%
5	$C(CO_2Me)_2$	CCl_3	10	60	24	**4e**, 44%
6	$C(CO_2Me)_2$	C_6F_5	5	60	1	**4f**, 67%
7	NTs	CO_2Et	2	60	0.5	**4g**, 75%
8	O	CO_2Et	2	60	2	**4h**, 49%

[a] All reactions were carried out with a nitrile (1.5 equiv.) in 1,2-dichloroethane under Ar. [b] Isolated yields.

present ruthenium-catalyzed pyridine annulation. In the presence of 10 mol% **1**, trichloroacetonitrile (**3g**) and pentafluorobenzonitrile (**3f**) were reacted with **2a** at 60 °C to afford pyridines **4e** and **4f** in 44 and 67% yields, respectively (entries 5 and 6). By employing *N*,*N*-dipropargyl tosylamide (**2b**) and dipropargyl ether (**2c**) as diyne components, 3-pyrroline- and 2,5-dihydrofuran-fused pyridines **4g** and **4h** were obtained in 75 and 49% yields, respectively (entries 7 and 8).

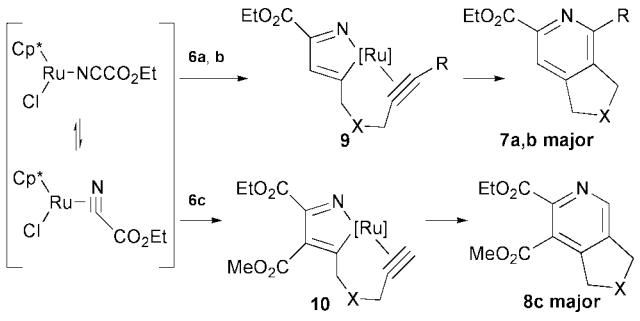
In order to establish the regiochemistry of the Ru(II)-catalyzed pyridine annulation, unsymmetrical 1,6-diynes **6a–c** were subjected to cycloaddition with **3a**, leading to 2,3,4,6-substituted isomers **7** and/or 2,3,4,5-substituted isomers **8** (Scheme 2). As a result, one of these isomers was predominantly obtained, depending on the nature of the alkyne substituents. In the presence of 5 mol% **1**, a octa-1,6-diyne **6a** (R = Me) reacted with **3a** at 60 °C for 2 h to afford a 88 : 12 mixture of **7a** and **8a** in 78% yield. The presence of an alkyl-substituent at the terminal position of the diyne decreased the reactivity. Similarly, the cycloaddition between a phenyl-substituted diyne **6b** (R = Ph) and **3a** was carried out using the 20 mol% catalyst at 60 °C. In this case, **7b** was isolated as a sole pyridine isomer in 50% yield. In contrast, the reaction of an ester **6c** and **3a** proceeded at rt and, unexpectedly, a 2,3-dialkoxycarbonyl isomer **8c** was obtained as a major product along with a minor isomer **7c** in 78% total yield. Therefore, the electron-



R = Me: 5 mol%, 60 °C, 2 h; 78% (**7a** : **8a** = 88 : 12)
R = Ph: 20 mol%, 60 °C, 6 h; 50% (**7b** : **8b** = 100 : 0)
R = CO_2Me: 5 mol%, r.t., 1 h; 78% (**7c** : **8c** = 13 : 87)

Scheme 2

 DOI: 10.1039/b102588k



Scheme 3

withdrawing ester group in **6c** reversed both the reactivity and the regioselectivity.

The origin of the observed regiochemistry and the difference in reactivity can be reasonably explained by the following mechanism (Scheme 3). The substituent on a nitrile component plays a critical role in the present protocol: electron-deficient nitriles having a carbonyl, sulfonyl, or polyhaloalkyl substituent gave rise to the desired pyridine product, although acetonitrile and benzonitrile gave little of the corresponding cycloadduct. This is probably because the electron-withdrawing group lowers the antibonding orbital level of the C–N triple bond to facilitate the oxidative cyclization involving the nitrile. In this situation, the catalytic cycle starts from the oxidative cyclization of a nitrile **3** and one alkyne terminus of a diyne **6** on the ruthenium center to form an azaruthenacyclopentadiene intermediate **9** or **10**. The regiochemistry of the product is determined in this stage. In the case of the alkyl- or aryl-substituted diynes **6a** and **6b**, the sterically less hindered terminal alkyne moiety can be favorably involved in the oxidative cyclization to form the intermediate **9**. The subsequent intramolecular alkyne insertion and reductive elimination steps afford the final pyridine product **7** as a major isomer. On the other hand, the diyne monoester **6c** forms predominantly the intermediate **10** because the oxidative cyclization occurs at the electron-deficient alkyne terminus due to its effective accommodation of the d-electron from the ruthenium center. As a result of the efficient formation of **10**, the cycloaddition of **6c** proceeded smoothly even at rt and gave **8c** as a major product.

We gratefully acknowledge financial support (10132222, 11119223, and 12450360) from the Ministry of Education, Science, Sports, and Culture, Japan.

Notes and references

‡ The IUPAC name for propargyl is prop-2-ynyl.

1 Y. Wakatsuki and H. Yamazaki, *J. Chem. Soc., Chem. Commun.*, 1973, 280; Y. Wakatsuki and H. Yamazaki, *J. Chem. Soc., Dalton. Trans.*, 1978, 1278.

2 For review, see: H. Bönnemen, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 248; K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 539; B. Grotjahn, in *Comprehensive Organometallic Chemistry II*, ed. L. S. Hegedus, E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, Oxford, 1995, vol. 12, pp. 741–770.

3 T. Takahashi, F.-Y. Tsai and M. Kotora, *J. Am. Chem. Soc.*, 2000, **122**, 4994.

4 A. Naiman and K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 708.

5 For other examples of the cycloaddition between α,ω-diynes and nitriles, see: Z. Zhou, L. P. Battaglia, G. P. Chiusoli, M. Costa, M. Nardelli, C. Pelizzi and G. Predieri, *J. Organomet. Chem.*, 1991, **417**, 51; G. P. Chiusoli, L. Pallini and G. Terenghi, *Transition Met. Chem.*, 1983, **8**, 250; L. P. Battaglia, D. Delledonne, M. Nardelli, G. Predieri, G. P. Chiusoli, M. Costa and C. Pelizzi, *J. Organomet. Chem.*, 1989, **363**, 209; G. Vitulli, S. Bertozzi, R. Lazzaroni and P. Salvadori, *J. Organomet. Chem.*, 1986, **307**, C35: G. Vitulli, S. Bertozzi, M. Vignali, R. Lazzaroni and P. Salvadori, *J. Organomet. Chem.*, 1987, **326**, C33.

6 C. A. Parnell and K. P. C. Vollhardt, *Tetrahedron*, 1985, **41**, 5791; R. E. Geiger, M. Lalonde, H. Stoller and K. Schleich, *Helv. Chim. Acta*, 1984, **67**, 1274.

7 For Cp*Ru(cod)Cl-catalyzed cycloadditions of 1,6-diynes, see: Y. Yamamoto, R. Ogawa and K. Itoh, *Chem. Commun.*, 2000, 549; Y. Yamamoto, H. Kitahara, R. Ogawa, H. Kawaguchi, K. Tatsumi and K. Itoh, *J. Am. Chem. Soc.*, 2000, **122**, 4310.