ORGANIC LETTERS

2011
Vol. 13, No. 12
3285–3287

Ruthenium-Catalyzed Regio- and Stereoselective Addition of Carboxylic Acids to Aryl and Trifluoromethyl Group Substituted Unsymmetrical Internal Alkynes

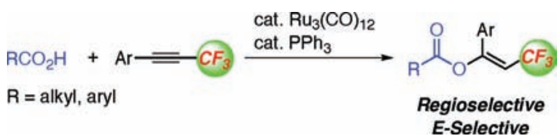
Motoi Kawatsura,* Junya Namioka, Koji Kajita, Mitsuaki Yamamoto, Hiroaki Tsuji, and Toshiyuki Itoh*

Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, Koyama, Tottori 680-8552 Japan

kawatsur@chem.tottori-u.ac.jp; titoh@chem.tottori-u.ac.jp

Received May 11, 2011

ABSTRACT



The regio- and stereoselective addition of carboxylic acids to aryl and trifluoromethyl group substituted unsymmetrical internal alkynes has been accomplished: the $Ru_3(CO)_{12}$/$3PPh_3$ catalyst system has effectively catalyzed the reaction to afford the trifluoromethyl group substituted (*E*)-enol esters with high regio- and stereoselectivities.

Enol esters are important compounds for organic synthesis and polymerization reactions, and one of the efficient methods to construct such a component is a transition-metal-catalyzed addition of carboxylic acid to alkynes. Although there are several transition-metal catalysts[1] that realize the addition of carboxylic acid to alkynes, ruthenium complexes are known as the most effective of these catalysts with which to conduct such a reaction.[2] The first example of a $Ru_3(CO)_{12}$-catalyzed addition reaction was reported by Shvo and Rotem in 1983.[3] After their pioneering work, several types of ruthenium catalysts were reported. For example, Dixneuf demonstrated $RuCl_3$ and other ruthenium complexes for catalyzing enol ester synthesis,[4] and Mitsudo et al. also described that a Ru(cod)$_2$/PBu_3/maleic anhydride catalyst system works for the addition reaction.[5] More recently, many groups attained highly regio- and/or *E*/*Z*-selective ruthenium-catalyzed

(1) For recent examples of transition-metal-catalyzed addition of carboxylic acid to alkynes, see: (a) Lumbroso, A.; Vautravers, N. R.; Breit, B. *Org. Lett.* **2010**, *12*, 5498–5501 and references cited therein. (b) Chary, B. C.; Kim, S. *J. Org. Chem.* **2010**, *75*, 7928–7931.

(2) Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; pp 189–217.

(3) (a) Rotem, M.; Shvo, Y. *Organometallics* **1983**, *2*, 1689–1691. (b) Rotem, M.; Shvo, Y. *J. Organomet. Chem.* **1993**, *448*, 189–204.

(4) (a) Ruppin, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1986**, *27*, 6323–6324. (b) Neveux, M.; Seiller, B.; Hagedorn, F.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1993**, *451*, 133–138. (c) Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1995**, *60*, 7247–7255. (d) Seiller, B.; Heins, D.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 10901–10912. (e) Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1997**, 507–512. (f) Doucet, H.; Derrien, N.; Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1997**, *551*, 151–157. (g) Emme, I.; Bruneau, C.; de Meijere, A.; Dixneuf, P. H. *Synlett* **2000**, 1315–1317.

(5) (a) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *Tetrahedron Lett.* **1986**, *27*, 2125–2126. (b) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230–2239. (c) Hori, Y.; Mitsudo, T.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *321*, 397–407.

(6) Leadbeater, N. E.; Scott, K. A.; Scott, L. J. *J. Org. Chem.* **2000**, *65*, 3231–3232.

(7) (a) Melis, K.; Samulkiewicz, P.; Rynkowski, J.; Verpoort, F. *Tetrahedron Lett.* **2002**, *43*, 2713–2716. (b) Opstal, T.; Verpoort, F. *Tetrahedron Lett.* **2002**, *43*, 9259–9263. (c) Opstal, T.; Verpoort, F. *Synlett* **2003**, 314–320. (d) Opstal, T.; Verpoort, F. *Synlett* **2002**, 935–941. (e) Melis, K.; Vos, D. D.; Jacobs, P.; Verpoort, F. *J. Organomet. Chem.* **2003**, *671*, 131–136.

(8) Goossen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706–707.

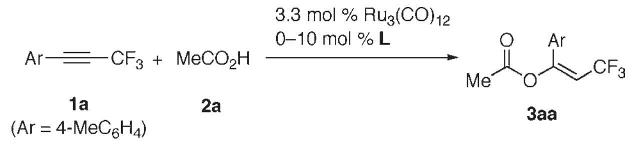
(9) Doherty, S.; Knight, J. G.; Rath, R. K.; Clegg, W.; Harrington, R. W.; Newman, C. R.; Campbell, R.; Amin, H. *Organometallics* **2005**, *24*, 2633–2644.

10.1021/ol201238u
Published on Web 05/23/2011

addition of carboxylic acids to alkynes.[6−15] However, most of the examples are limited to the reaction of terminal alkynes or symmetrical internal alkynes. To the best of our knowledge, there is only one example of the ruthenium-catalyzed addition of carboxylic acid to an unsymmetrical internal alkyne: Shvo and co-workers examined the addition reaction of benzoic acid to 1-phenyl-1-heptyne, but the reaction yielded a mixture of more than four stereoisomers.[3b] During the course of our research on the ruthenium-catalyzed trimerization of trifluoromethyl group-substituted internal alkynes,[16] we observed the formation of enol esters when carboxylic acid was added to the reaction mixture. The result strongly encouraged us to investigate the ruthenium-catalyzed stereoselective addition of carboxylic acid to aryl and trifluoromethyl group substituted unsymmetrical internal alkynes; we succeeded in obtaining the trifluoromethyl group substituted enol esters with high regio- and stereoselectivities.

We examined the addition reaction of acetic acid (**2a**) to *p*-tolyl and trifluoromethyl group substituted internal alkyne **1a** using ruthenium catalysts (Table 1). Based on the observation of our previous ruthenium-catalyzed trimerization of **1a**, we tested the addition of **2a** to **1a** by $Ru_3(CO)_{12}$ with 2-(diphenylphosphino) benzonitrile (2-DPPBN). The reaction at 80 °C in CH_3CN gave the expected trifluoromethyl group-substituted enol esters **3aa**, but the yield was miserable (entry 1). To our delight, optimization of the catalysts afforded desired enol ester: the PPh_3- or DPPB-ligated ruthenium catalysts exhibit good catalyst activity against the desired reaction (entries 3 and 4). The yields were improved by raising the reaction temperature to 100 °C (entries 5−9). In particular, the PPh_3-ligated ruthenium catalyst gave the best results, and 80% of the desired product was then obtained as a single stereoisomer (entry 8).[17] Toluene also worked as a good solvent for this reaction, but the dioxane solvent system gave a better result than did toluene (entries 8 and 9). We further observed that the reaction proceeded with high regio- and *E*-selectivities.[18,19]

Table 1. Ruthenium-Catalyzed Addition of Acetic Acids **2a** to **1a**[a]



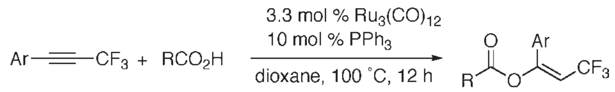
entry	L	solvent	temp (°C)	yield[b] (%)
1	2-DPPBN	CH_3CN	80	32
2		CH_3CN	80	28
3	DPPB	CH_3CN	80	60
4	PPh_3	CH_3CN	80	67
5	2-DPPBN	dioxane	100	63
6		dioxane	100	67
7	DPPB	dioxane	100	67
8	PPh_3	dioxane	100	80 (73)[c]
9	PPh_3	toluene	100	71

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), 3.3 mol % of $Ru_3(CO)_{12}$, ligand (10 mol % for PPh_3, 5 mol % for 2-DPPBN and DPPB), 0.5 mL of solvent, 12 h. [b] The yields were determined by ^1H NMR using an internal standard (trioxane). [c] Isolated yield is shown in parentheses.

We next demonstrated the $Ru_3(CO)_{12}/3PPh_3$-catalyzed addition of several carboxylic acids **2b**−**o** to aryl and trifluoromethyl group substituted unsymmetrical internal alkynes **1a**−**e**, and the results are summarized in Table 2. Typically, the reaction was carried out as follows: 3.3 mol % of $Ru_3(CO)_{12}$, 10 mol % of PPh_3, alkyne **1**, and carboxylic acid **2** (1.0 equiv) were mixed in dioxane at 100 °C for 12 h. The addition of benzoic acid (**2b**) to **1a** under optimized conditions formed the desired enol ester **3ab** in 89% isolated yield without formation of byproduct (entry 1). We also confirmed that the amount of ruthenium catalyst could be reduced to 1.1 mol % of $Ru_3(CO)_{12}$ and 3.3 mol % of PPh_3 without decreasing the yield (entry 2). Benzoic acid analogues, which have the electron-donating group on the aromatic ring, provided the desired products **3ac**−**af** (entries 3−6) (Figure 1). On the other hand, an electron-withdrawing group also did not influence the result, and the desired enol esters were obtained in good yields (entries 7−9). The sterically hindered aromatic carboxylic acids, such as 1-naphthoic acid (**2j**) and *ortho*-substituted benzoic acid analogues **2k**−**m**, gave trifluoromethyl group substituted internal enol esters **3aj**−**am** in good yield (entries 10−14), and even the reaction with 2,6-dimethylbenzoic acid (**2n**) formed the product **3an** in 70% isolated yield (entry 14). To our delight, we confirmed that the ruthenium catalyst systems exhibit good catalyst activity for the reaction of aliphatic carboxylic acid (entries 15 and 16). We further succeeded in obtaining the desired product in the addition of benzoic acid to several aryl and trifluoromethyl group containing internal alkynes (**1b**−**e**) with good to high yields (entries 17−20). Those results clearly indicate that the reaction is applicable to reactions using various combinations of carboxylic acid and 1-aryl-3,3,3-trifluoropropynes.

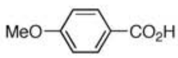
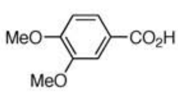
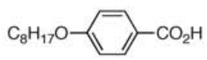
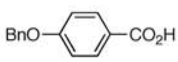
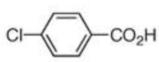
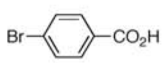
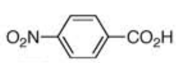
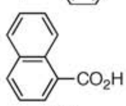
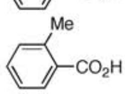
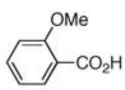
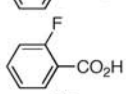
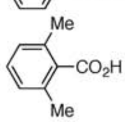
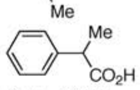
(10) Ye, S.; Leong, W. K. *J. Organomet. Chem.* **2006**, *691*, 1117–1120.
(11) Pelagatti, P.; Bacchi, A.; Balordi, M.; Bolaño, S.; Calbiani, F.; Elviri, L.; Gonsalvi, L.; Pelizzi, C.; Peruzzini, M.; Rogolino, D. *Eur. J. Inorg. Chem.* **2006**, 2422–2436.
(12) (a) Yi, C. S.; Gao, R. *Organometallics* **2009**, *28*, 6585–6592. (b) Yi, C. S. *J. Organomet. Chem.* **2011**, *696*, 76–80.
(13) Tripathy, J.; Bhattacharjee, M. *Tetrahedron Lett.* **2009**, *50*, 4863–4865.
(14) Tan, S. T.; Fan, W. Y. *Eur. J. Inorg. Chem.* **2010**, 4631–4635.
(15) Cadierno, V.; Francos, J.; Gimeno, J. *Organometallics* **2011**, *30*, 852–862.
(16) Kawatsura, M.; Yamamoto, M.; Namioka, J.; Kajita, K.; Hirakawa, T.; Itoh, T. *Org. Lett.* **2011**, *13*, 1001–1003.
(17) We confirmed the formation of 3,3,3-trifluoro-1-tolylpropan-1-one as a byproduct (< 10%), and the structure of it was determined by comparison with reported NMR data; see: (a) Kamitoi, Y.; Hojo, Y.; Masuda, R.; Ohara, S.; Kawamura, Y.; Ebisu, T. *Synthesis* **1989**, 43–45. (b) Laurent, A. J.; Lesniak, S. *Tetrahedron Lett.* **1992**, *33*, 3311–3314.
(18) Regioselectivity (> 20:1) and *E*-selectivity (> 20:1) were determined by ^1H and ^{19}F NMR of the crude materials.
(19) The stereochemistry of **3aa** was determined by comparison of the X-ray crystallographic analysis of the product **3ad**.

Table 2. $Ru_3(CO)_{12}/PPh_3$-Catalyzed Addition of Carboxylic Acids **2b**−**p** to Trifluoromethyl Group Substituted Alkynes **1a**−**e**[a]



1a: Ar = 4-MeC_6H_4 **2b-p**
1b: Ar = C_6H_5
1c: Ar = 4-$MeOC_6H_4$
1d: Ar = 4-ClC_6H_4
1e: Ar = 2-$MeOC_6H_4$

3

entry	1	2	yield (%)[b,c]
1	**1a**	$PhCO_2H$ **2b**	89
2[d]			89
3	**1a**	 **2c**	74
4	**1a**	 **2d**	81
5	**1a**	 **2e**	88
6	**1a**	 **2f**	81
7	**1a**	 **2g**	86
8	**1a**	 **2h**	87
9	**1a**	 **2i**	67 (82)
10	**1a**	 **2j**	84 (94)
11	**1a**	 **2k**	81
12	**1a**	 **2l**	84
13	**1a**	 **2m**	82 (91)
14	**1a**	 **2n**	70
15	**1a**	 **2o**	82
16	**1a**	$C_{19}H_{39}CO_2H$ **2p**	82
17	**1b**	$PhCO_2H$ **2b**	87
18	**1c**	$PhCO_2H$ **2b**	91
19	**1d**	$PhCO_2H$ **2b**	92
20	**1e**	$PhCO_2H$ **2b**	78

[a] Reaction conditions: **1a**−**e** (1.00 mmol), **2b**−**p** (1.00 mmol), 3.3 mol % of $Ru_3(CO)_{12}$, and 10 mol % of PPh_3 in dioxane (0.5 mL) at 100 °C for 12 h. [b] Isolated yield. [c] NMR yield is in parentheses. [d] 1.1 mol % of $Ru_3(CO)_{12}$ and 3.3 mol % of PPh_3 were used.

The reaction proceeded with high regio- and *E*-selectivity. Although the details of the reaction mechanism, including the origin of the stereoselectivities and the influence of the trifluoromethyl group, have not yet been clarified, we currently believe that the reaction proceeds as follows (Scheme 1). The ruthenium complex **I**, which may be formed from $Ru_3(CO)_{12}/3PPh_3$ and carboxylic acid, smoothly constructs complex **II** via coordination of **1** and migratory insertion. The selective formation of **II** is a critical step in realizing the high regioselectivity, and the following oxidative addition of **2** and reductive elimination of the enol ester proceeds with *E*-selectivity. Further study of the mechanistic details will be the subject of a future study.

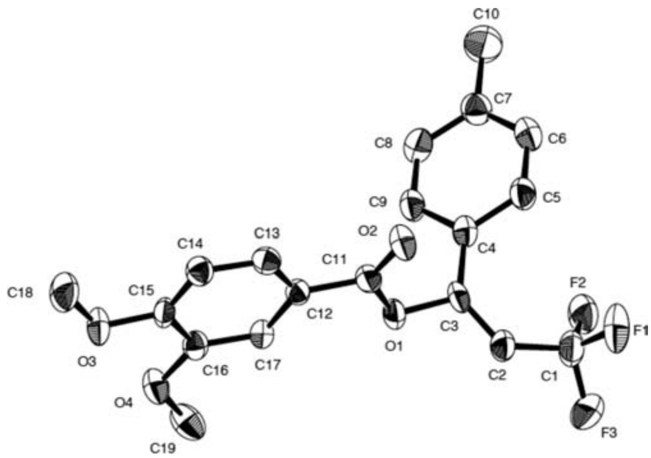
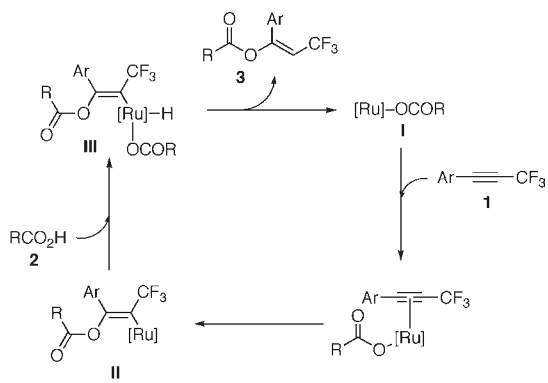


Figure 1. Molecular structure of **3ad**.

Scheme 1. Plausible Catalytic Cycle



In conclusion, we demonstrated the highly regio- and *E*-selective formation of trifluoromethyl group containing enol esters by ruthenium-catalyzed addition of carboxylic acid to aryl and trifluoromethyl group substituted unsymmetrical internal alkynes. The reaction proceeded with several carboxylic acids and provided the desired enol esters in good yield. Further investigation of the scope and limitation of this reaction will make it even more valuable.

Supporting Information Available. Experimental details, characterization data, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.