ORGANIC LETTERS

2010
Vol. 12, No. 23
5498−5501

Rhodium-Catalyzed Selective *anti*-Markovnikov Addition of Carboxylic Acids to Alkynes

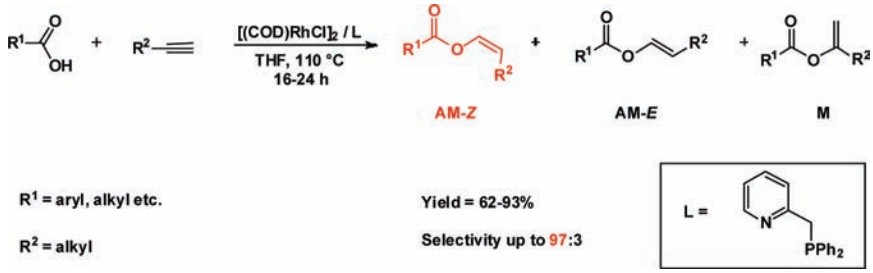
Alexandre Lumbroso, Nicolas R. Vautravers, and Bernhard Breit*

Institut für Organische Chemie und Biochemie, Freiburg Institute for Advanced Studies (FRIAS), Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, 79104, Freiburg, Germany

bernhard.breit@chemie.uni-freiburg.de

Received October 1, 2010

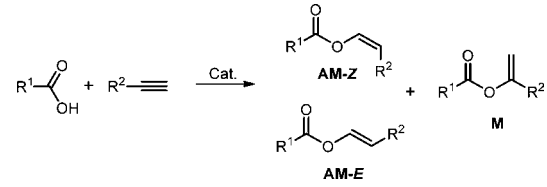
ABSTRACT



The selective intermolecular *anti*-Markovnikov addition of carboxylic acids to terminal alkynes yielding valuable *Z*-enol esters has been achieved for the first time under rhodium-catalyzed conditions. The catalyst system is applicable to a broad substrate scope and displays a wide functional group tolerance.

Transition metal-catalyzed addition of carboxylic acids to terminal alkynes is an efficient and atom-economic method for the preparation of 1-alkenyl esters, which are widely used as monomers for polymerization[1] and mild acylating agents.[2] Since Shvo and co-workers reported the first example of such a reaction in 1983 using $Ru_3(CO)_{12}$ as catalyst,[3] most significant improvements have been attained employing ligand modified ruthenium to furnish selectively either the Markovnikov (M) and/or *anti*-Markovnikov (AM-*Z*, AM-*E*) enol esters with high levels of regio- and stereocontrol (Scheme 1).[4] Other metals like iridium[5] and rhenium[6] have also been used as catalysts for the intermolecular reaction whereas rhodium[7] or palladium[8] have mainly been applied for the intramolecular process yielding alkylidene lactones.

Scheme 1. Addition of Carboxylic Acids to Terminal Alkynes



A single report on a polyphosphine modified rhodium catalyst is known which allows for intermolecular Markovnikov-selective addition of carboxylic acids to terminal alkynes.[9] Herein, we disclose the first selective rhodium-catalyzed intermolecular *anti*-Markovnikov addition of carboxylic acids

(1) Montheard, J. P.; Camps, M.; Seytre, G.; Guillet, J.; Dubois, J. C. *Angew. Makromol. Chem.* **1978**, *72*, 45–55.

(2) (a) Bruneau, C.; Neveux, M.; Kabouche, Z.; Ruppin, C.; Dixneuf, P. H. *Synlett* **1991**, 755–763. (b) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567–4571. (c) Quirin, C.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, *48*, 371–377.

(3) Rotem, M.; Shvo, Y. *Organometallics* **1983**, *2*, 1689–1691.

10.1021/ol102365e
Published on Web 11/04/2010

to terminal alkynes yielding valuable *Z*-enol esters employing a new rhodium catalyst.

As a model system, we studied the reaction of benzoic acid with 1-octyne employing $[(COD)RhCl]_2$ [COD = 1,5-cyclooctadiene] as the catalyst precursor in the presence of donor ligands (Table 1).

Table 1. Optimization of Hydro-oxycarbonylation Conditions[a]

entry	ligand	solvent	AM-Z/AM-E/M[b]	% yield[c]
1	PPh_3	THF	46/22/32	28
2	DPPE	THF	14/8/78	24
3	DPPP	THF	22/5/73	<10
4	DPPB	THF	64/4/32	21
5	–	THF	n.d.	<5
6[d]	–	THF	72/16/12	79
7[e]	Ph_3P/Py	THF	45/25/30	36
8[f]	L	THF	94/3/3	90
9[g]	DPP	THF	33/31/36	<10
10	L	Et_2O	44/12/44	<10
11	L	CH_2Cl_2	37/22/41	<10
12	L	toluene	51/13/36	18
13[h]	L	THF	21/37/42	40
14[i]	L	THF	40/27/33	60

[a] Reaction conditions: 0.0044 mmol of $[(COD)RhCl]_2$, 0.0088 mmol of ligand, 0.44 mmol of benzoic acid, and 0.66 mmol of 1-octyne in 400 μL of solvent were heated in a closed Schlenk vessel at 110 °C for 16 h. [b] Determined by integration of the ethylenic protons in the crude ^1H NMR (see the Supporting Information). [c] Isolated yields. [d] $[RhCl(PPh_3)_3]$ was used as rhodium precursor. [e] $[(COD)RhCl]_2/PPh_3$/Py = 1/1/1 [Py = pyridine]. [f] Determined by integration of the ethylenic protons in the crude ^1H NMR and GC analyses. [g] [DPP = diphenyl(2-pyridyl)phosphine]. [h] $[(COD)IrCl]_2$ was used as catalyst. [i] $[(COD)RuCl_2]$ was used as catalyst. [COD = cyclooctadiene].

Poor yields were obtained in THF at 110 °C upon moving from the monodentate PPh_3 (28%, entry 1) to the bidentates dppe, dppp, and dppb (24%, <10%, and 21%, respectively, entries 2−4), with a notable change in the regioselectivity within the latter family: *anti*-Markovnikov product being favored with dppb as opposed to the gem-enol ester type product observed with dppe. Similar observations have already been made by Dixneuf and co-workers using (bis(diphenylphosphino)alkane)Ru(η^3-methallyl)$_2$ as the catalyst.[4b] While the reaction did not proceed without ligand (yield <5%, entry 5), the use of Wilkinson's catalyst significantly enhanced both the regioselectivity in favor of the *Z-anti*-Markovnikov product (72/16/12, AM-*Z*/AM-*E*/M) and the rate of the reaction (79% yield, entry 6). Goossen et al. found that the addition of catalytic amounts of pyridine or DMAP to a ruthenium catalyst generated in situ from $((p\text{-cumene})RuCl_2)_2$ and P(p-Cl-C_6H_4)$_3$ favored the formation of AM-*Z*.[10] Unfortunately, addition of pyridine in the presence of $[(COD)RhCl]_2$ and PPh_3 did not furnish a more selective catalyst (entry 7). However, when employing a ligand that combines a pyridine moiety and a diphenylphosphine donor function, 2-(diphenylphosphinomethyl)pyridine (**L**), high yield (90%) and regioselectivity (94/3/3, AM-*Z*/AM-*E*/M) were reached (entry 8). The reaction has been run on a 5 mmol scale giving slightly better yield (93%) and the same selectivity as the standard conditions (entry 8). Ligand **L** can be easily prepared on a gram-scale starting from 2-picoline and chlorodiphenylphosphine in two steps.[11] Interestingly, using diphenyl(2-pyridyl)phosphine (DPP) as the ligand did not furnish an efficient catalyst (entry 9). This suggests that ligand **L** acts as a chelating ligand via P/N-coordination. A quick screen of suitable solvents revealed THF to be the optimal in terms of catalyst activity and selectivity (entries 8 and 10−12). Similar strong solvent effects have previously been observed for the ruthenium hydride $(PCy_3)_2(CO)RuHCl$ catalyst system.[12] Changing the metal precursor from rhodium to iridium or ruthenium was deleterious (entries 13 and 14, respectively).

With a highly active catalyst system in hand (Table 1, entry 8), we explored the substrate scope of the reaction (Table 2). Reasonable yields and regioselectivities ranging from 90% to 65% and 94/3/3 to 77/−/23, respectively, were obtained for the addition of various terminal alkynes to benzoic acid, with better yields for less hindered substrates (entries 1−4). No reaction was observed with phenylacetylene, which is usually converted in good yields with other metals (entry 5).[4−6,10] Both electron-donating as well as electron-withdrawing substituents at the aryl carboxylic acid system were well tolerated (entries 6−12). Even an unprotected phenol function was compatible with the reaction conditions (entry 10). Furthermore, heterocycle-based carboxylic acids (entries 13 and 14), aliphatic acids (entries 15 and 16), unsaturated acids (entries 17 and 18), and *N*-carbamoyl-protected α-amino acids (entries 19 and 20) were efficient reaction partners, thus highlighting the wide functional group tolerance of this catalyst system.

Taking into account that internal alkynes do not show reactivity with our rhodium-catalyst system together with the *anti*-Markovnikov selectivity observed in this reaction, a reaction mechanism involving a rhodium vinylidene species is most likely (Scheme 2). The first step is the

(4) (a) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230–2239. (b) Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1995**, *60*, 7247–7255. (c) Le Paih, J.; Monnier, F.; Dérien, S.; Dixneuf, P. H.; Clot, E.; Eisenstein, O. *J. Am. Chem. Soc.* **2003**, *125*, 11964–11975. (d) Melis, K.; Samulkiewicz, P.; Rynkowski, J.; Verpoort, F. *Tetrahedron Lett.* **2002**, *43*, 2713–2716. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159. (f) Drozdzak, R.; Allaert, B.; Ledoux, N.; Dragutan, I.; Dragutan, V.; Verpoort, F. *Adv. Synth. Catal.* **2005**, *347*, 1721–1743. (g) Nicks, F.; Aznar, R.; Sainz, D.; Muller, G.; Demonceau, A. *Eur. J. Org. Chem.* **2009**, 5020–5027.

(5) Nakagawa, H.; Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 103–106.

(6) Hua, R.; Tian, X. *J. Org. Chem.* **2004**, *69*, 5782–5784.

(7) (a) Chan, D. M. T.; Marder, T. B.; Milstein, D.; Taylor, N. J. *J. Am. Chem. Soc.* **1987**, *109*, 6385–6388. (b) Elgafi, S.; Field, L. D.; Messerle, B. A. *J. Organomet. Chem.* **2000**, *607*, 97–104. (c) Mas-Marzá, E.; Sanaù, M.; Peris, E. *Inorg. Chem.* **2005**, *44*, 9961–9967.

(8) (a) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323–5326. (b) Wolf, L. B.; Tjen, K. C. M. F.; ten Brink, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 70–83. (c) Wang, Y.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 3859–3862.

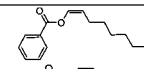
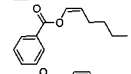
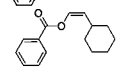
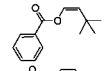
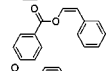
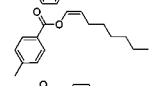
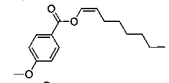
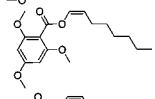
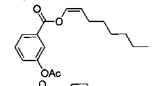
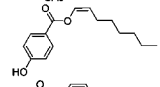
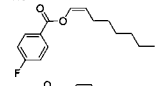
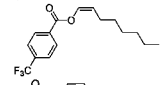
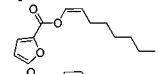
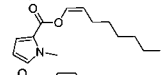
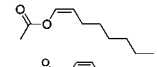
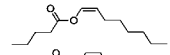
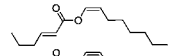
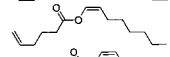
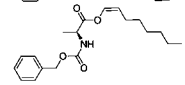
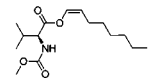
(9) Bianchini, C.; Meli, A.; Peruzzini, M.; Zanobini, F.; Bruneau, C.; Dixneuf, P. H. *Organometallics* **1990**, *9*, 1155–1160.

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

(11) Kermagoret, A.; Braunstein, P. *Organometallics* **2008**, *27*, 88–99.

(12) Yi, C. S.; Gao, R. *Organometallics* **2009**, *28*, 6585–6592.

Table 2. Intermolecular Hydro-oxycarbonylation of Terminal Alkynes under Rhodium-Catalyzed Conditions[a]

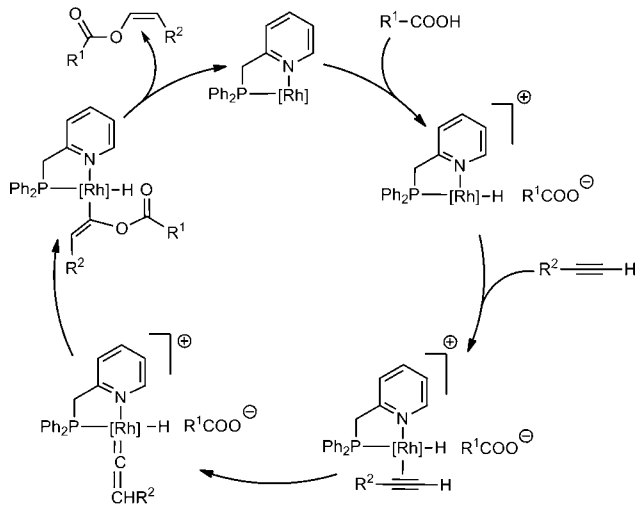
Entry[a]	R^1	R^2	Time	Product		AM-*Z*/AM-*E*/M[b]	% Yield[c]
1	C_6H_5	*n*-C_6H_{13}	16	**1a**		94/3/3	90
2	C_6H_5	*n*-C_4H_9	16	**1b**		94/3/3	83
3	C_6H_5	Cyclohexyl	16	**1c**		85/4/11	65
4	C_6H_5	*t*-Butyl	16	**1d**		77/-/23	73
5	C_6H_5	C_6H_5	16	-		n.d.	<5
6	*p*-Me(C_6H_4)	*n*-C_6H_{13}	16	**2**		94/2/4	92
7	*p*-OMe(C_6H_4)	*n*-C_6H_{13}	16	**3**		96/-/4	93
8	2,4,6-$(OMe)_3(C_6H_2)$	*n*-C_6H_{13}	16	**4**		95/-/5	88
9	*m*-AcO(C_6H_4)	*n*-C_6H_{13}	16	**5**		95/-/5	81
10	*p*-HO (C_6H_4)	*n*-C_6H_{13}	16	**6**		87/2/11	73
11	*p*-F(C_6H_4)	*n*-C_6H_{13}	16	**7**		94/2/4	83
12	*p*-$CF_3(C_6H_4)$	*n*-C_6H_{13}	16	**8**		77/-/23	81
13	2-furyl	*n*-C_6H_{13}	16	**9**		93/3/4	95
14	1-Me-pyrrol-2-yl	*n*-C_6H_{13}	16	**10**		97/-/3	92
15	CH_3	*n*-C_6H_{13}	24	**11**		97/-/3	70
16	*n*-C_4H_9	*n*-C_6H_{13}	24	**12**		97/-/3	85
17[d]	*n*-$C_3H_7(C_2H_2)$	*n*-C_6H_{13}	24	**13**		96/-/4	74
18	*n*-$C_2H_3(C_3H_6)$	*n*-C_6H_{13}	24	**14**		96/-/4	83
19	*N*-Cbz-*L*-alanine	*n*-C_6H_{13}	24	**15**		85/-/15	71
20	*N*-Moc-*L*-valine	*n*-C_6H_{13}	24	**16**		91/-/9	62

[a] Reaction conditions: 0.0044 mmol of $[(COD)RhCl]_2$, 0.0088 mmol of **L**, 0.44 mmol of acid, and 0.66 mmol of alkyne in 400 μL of THF were heated in a closed Schlenk vessel at 110 °C. [b] Determined by GC analyses and integration of the ethylenic protons in the crude ^{1}H NMR (see the Supporting Information). [c] Isolated yields. [d] 0.022 mmol of catalyst was used. [COD = cyclooctadiene].

oxidative addition of the carboxylic acid to the Rh(I) center as the prevalence of O−H oxidative addition over the C−H one of terminal alkynes has already been demonstrated.[9] η^2-Coordination of the alkyne to the metal was followed by rearrangement to an η^1-vinylidene-rhodium species, which was then attacked by the carboxylic acid at the more electrophilic carbon atom.[13] Reductive elimination liberates the *Z-anti*-Markovnikov product and regenerates the catalyst.[13a] The *Z* stereochemistry would be preferred in order to minimize the steric repulsion between the R^2 group and the bulky rhodium catalyst, in agreement with observations from Mistudo[14] and Dixneuf[15] employing ruthenium catalysts.

(13) (a) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311–323. (b) Park, Y. J.; Kwon, B.-I.; Ahn, J.-A.; Lee, H.; Jun, C.-H. *J. Am. Chem. Soc.* **2004**, *126*, 13892–13893.

Scheme 2. Proposed Mechanism for the Hydro-oxycarbonylation of Terminal Alkynes under Rhodium-Catalyzed Conditions in the Presence of **L**



In summary, we have developed the first rhodium catalyst for the intermolecular hydro-oxycarbonylation of terminal alkynes to furnish the corresponding *Z-anti*-Markovnikov enol esters in good to high yields and excellent stereoselectivities. The catalyst system is applicable to a broad substrate scope and displays a wide functional group tolerance.

Acknowledgment. This work was supported by the DFG, the International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis" (IRTG 1038), the Fonds der Chemischen Industrie, the Krupp Foundation (Alfried Krupp Award for young university teachers to B.B.), and the Humboldt Foundation (postdoctoral fellowship to N.R.V.). We thank Umicore, BASF, and Wacker for generous gifts of chemicals.

Supporting Information Available: Detailed experimental procedures, characterizations, and copies of NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102365E

(14) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *38*, 4417–4418.
(15) Mahe, R.; Sasaki, Y.; Bruneau, D.; Dixneuf, P. H. *J. Org. Chem.* **1989**, *54*, 1518–1523.