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Regioselective control of the thiocarbonylation of terminal acetylenes with arylthiols catalyzed by Pd(II) and diphosphine ligands

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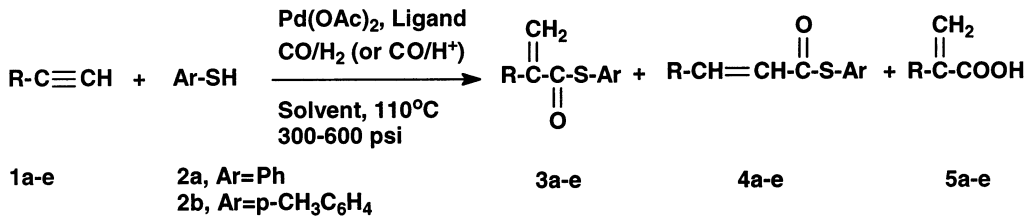
Abstract—Control of the regioselective thiocarbonylation of terminal acetylenes **1a–e** with arylthiols **2a,b** was successfully achieved by using $Pd(OAc)_2$ and 1,4-bis(diphenylphosphino)butane (dppb), or 1,3-bis(diphenylphosphino)propane (dppp), as catalysts. The formation of the thioesters **3** or **4** depends mainly on the type of ligand (dppp or dppb) and the solvent (THF or CH_2Cl_2) under CO/H^+ or syngas mixture.

The transition-metal-catalyzed carbonylation of organic sulfur compounds has been the subject of a few investigations.[1,2] A variety of transition metal complexes has been used as catalysts in the carbonylation of different sulfur-containing compounds.[3,4] A series of transition-metal-catalyzed addition and carbonylation–addition reactions of organic disulfides and thiols to acetylenes leading to α,β-unsaturated thioesters has been developed.[5–7] Recently, Alper and co-workers have introduced new interesting methods of palladium-catalyzed thiocarbonylation of various alkynes.[8,9] The thioesters represent attractive building blocks in the synthesis of various complex molecules.[10] The search for new methodology for the synthesis of *gem*- and *trans*-α,β-unsaturated thioesters is of high interest. We have now examined the carbonylative addition of arylthiols to terminal acetylenes in the presence of palladium(II) catalysts and different phosphine ligands. $Pd(OAc)_2$ was found to exhibit excellent catalytic activity and regioselectivity toward thioester **3** or **4** depending on the type of the phosphine ligand, the solvent, and the additive (Eq. (1)).

The thiocarbonylation of 1-heptyne ($R = C_6H_{13}$) with thiophenol ($Ar = Ph$) was chosen as a model reaction and was carried out by changing the type of catalyst, ligand, solvent, and additive.[15] The results are summarized in Table 1. No product of carbonylation was obtained in the absence of *p*-TsOH (Table 1, entry 1). The initial reaction conditions screening indicated that the use of the catalytic system $Pd(OAc)_2$/dppp/CO/*p*-TsOH/THF (**A**) affords the thioester **3b** as the main product (Table 1, entry 2). Important loss of selectivity or catalytic activity has been observed by replacing *p*-TsOH with other additives such as PhCOOH or CH_3SO_3H (Table 1, entries 3 and 4), or replacing dppp in **A** with other bidentate ligands such as dppb or monodentate phosphine ligand such as PPh_3 (Table 1, entries 7 and 8), or by using $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ in place of $Pd(OAc)_2$ (Table 1, entries 8 and 9).

In addition, a significant decrease in the catalytic activity and/or the selectivity was observed when toluene, CH_2Cl_2, CH_3CN, or hexane was used in place of THF. Also, the use of 300 psi of H_2 in place of *p*-TsOH



(1)

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Table 1. Palladium (II)-catalyzed thiocarbonylation of 1-heptyne with thiophenol[a]

Entry	Catalyst	Ligand	Solvent	H^+ (mmol)	CO (psi)	H_2 (psi)	Yield[b] (%) (**3b**+**4b**)	Product distribution[c] (%)		Yield[b] **5b** (%)
								3b	**4b**	
1	$Pd(OAc)_2$	dppp	THF	–	300	–	Traces	–	–	–
2	$Pd(OAc)_2$	dppp	THF	*p*-TsOH (0.04)	300	–	87	100	–	12
3	$Pd(OAc)_2$	dppp	THF	*p*-TsOH (0.12)	300	–	61	100	–	32
4	$Pd(OAc)_2$	dppp	THF	PhCOOH (0.04)	300	–	96	68	32	2
5	$Pd(OAc)_2$	dppp	THF	CH_3SO_3H (0.04)	300	–	55	100	–	15
6[d]	$Pd(OAc)_2$	dppp	THF	*p*-TsOH (0.04)	300	–	77	95	5	15
7	$Pd(OAc)_2$	dppp	THF	*p*-TsOH (0.04)	300	–	64	72	28	11
8	$Pd(OAc)_2$	PPh_3	THF	*p*-TsOH (0.04)	300	–	13	69	31	–
9	$PdCl_2(PPh_3)_2$	dppp	THF	*p*-TsOH (0.04)	300	–	50	76	24	8
10	$Pd(PPh_3)_4$	dppp	THF	*p*-TsOH (0.04)	300	–	74	64	36	5
11	$Pd(OAc)_2$	dppp	THF	–	300	300	40	62	38	15
12	$Pd(OAc)_2$	dppb	THF	–	300	300	30	52	48	–
13	$Pd(OAc)_2$	dppb	CH_2Cl_2	–	300	300	96	21	79	32
14	$Pd(OAc)_2$	dppp	CH_2Cl_2	–	600	–	Traces	–	–	–
15	$Pd(OAc)_2$	dppp	CH_2Cl_2	–	100	500	95	24	76	–
16	$Pd(OAc)_2$	dppp	CH_2Cl_2	–	500	100	92	25	75	–
17	$Pd(OAc)_2$	dppb	CH_2Cl_2	–	100	100	47	60	40	–
18	$Pd(OAc)_2$	dppb	THF	–	100	100	30	52	48	–
19	$PdCl_2(PPh_3)_2$	dppb	CH_2Cl_2	–	300	300	65	66	34	–
20	$Pd(PPh_3)_4$	dppb	CH_2Cl_2	–	300	300	84	43	57	–

[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), ligand (0.08 mmol), 1-heptyne (2.0 mmol), thiophenol (2.0 mmol), solvent (10 ml), 6 h (entries 1–9) and 24 h (entries 10–19).
[b] Isolated yields.
[c] The ratio **3**/**4** was determined by GC and ^1H NMR.
[d] 120°C.

affects the yield and the selectivity of the reaction (Table 1, entry 11). It is important to note that the presence of *p*-TsOH and dppp enhances the formation of the α,β-unsaturated carboxylic acid **5b** (Table 1, entries 2, 3, 5–7, 9, and 15). The origin of **5b** is probably from the direct hydrocarboxylation of alkynes in the presence of *p*-TsOH as additive,[11] and/or from the acid hydrolysis of thioester **3b**. Interestingly, the catalytic system including $Pd(OAc)_2$/dppb/CO/H_2/CH_2Cl_2 (**B**) gave *trans*-thioesters **4b** as the major products (Table 1, entry 13). No reaction was observed in the absence of H_2 (Table 1, entry 14). Low total yields and selectivities toward **4b** were obtained by using THF in place of CH_2Cl_2 (Table 1, entry 12). The change of the CO/H_2 ratio did not affect the selectivity of the reaction. A lower total pressure of 200 psi (CO/H_2= 1:1) decreases the total yield as well the selectivity (Table 1, entry 17). The use of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ in place of $Pd(OAc)_2$ decreases the catalytic activity of system **B**.

The results of the carbonylation of different alkynes **1a–e** with arylthiols **2a**,**b** are summarized in Table 2. The representative results of the catalytic thiocarbonylation of different terminal acetylenes and arylthiols showed excellent control of the regioselectivity of the thiocarbonylation of thiophenol **2a** and 4-methylbenzenethiol **2b** with 1-pentyne and 1-heptyne (Table 2, entries 1–8) in the presence of the catalytic system **A** or **B**. The selectivity of **3** is almost independent of the electronic and steric effects of the group attached to the terminal acetylene. However, low total yields of thioesters were obtained with **1c** due probably to a steric effect (Table 2, entries 9 and 11). The selectivity of the thioester **4** is strongly sensitive to the steric effect (Table 2, entries 10 and 12) and to the electronic effect of the substituent (Table 2, entries 14, 16, and 18). The steric and electronic effects of the substituent groups have been previously observed in different hydrocarboxylation reactions of alkynes.[11–14] The mechanism of the formation of *gem*-α,β-unsaturated thioesters is probably similar to those proposed for the hydrocarboxylation of alkynes;[11,14] however, the mechanism of the selective formation of the *trans*-thioesters **4** is still under investigation.

In conclusion, we have developed novel palladium(II) catalyst systems that allow total control of the regioselectivity of the thiocarbonylation of terminal alkynes with arylthiols and provide significant improvement over the current systems. Both catalyst systems **A** and **B** have $Pd(OAc)_2$ as the catalyst and can be easily selected by changing the ligand, solvent, and by using CO/additive or syngas.

Table 2. Palladium (II)-catalyzed thiocarbonylation of terminal acetylenes with arylthiols[a]

Entry	Alkyne R (**1**)	Thiol **2**	Catalytic system[b]	Yield[c] (**3**+**4**) (%)	Product distribution[d] (%)		Yield[c] **5a–e** (%)
					3a–e	**4a–e**	
	$CH_3CH_2CH_2$ (**1a**)						
1	**1a**	**2a**	**A**	86	100	–	8
2	**1a**	**2a**	**B**	93	15	85	–
3	**1a**	**2b**	**A**	88	100	–	10
4	**1a**	**2b**	**B**	96	17	83	–
	$CH_3(CH_2)_3CH_2$ (**1b**)						
5	**1b**	**2a**	**A**	87	100	–	12
6	**1b**	**2a**	**B**	96	21	79	–
7	**1b**	**2b**	**A**	82	100	–	12
8	**1b**	**2b**	**B**	90	20	80	–
	$(CH_3)_3C$ (**1c**)						
9	**1c**	**2a**	**A**	25	71	29	7
10	**1c**	**2a**	**B**	95	–	100	–
11	**1c**	**2b**	**A**	13	77	23	10
12	**1c**	**2b**	**B**	90	–	100	–
	$CNCH_2CH_2CH_2$ (**1d**)						
13	**1d**	**2a**	**A**	85	100	–	13
14	**1d**	**2a**	**B**	96	37	63	–
15	**1d**	**2b**	**A**	84	100	–	10
16	**1d**	**2b**	**B**	98	33	67	–
	Ph (**1e**)						
17	**1e**	**2a**	**A**	84	100	–	15
18	**1e**	**2a**	**B**	75	65	35	–

[a] Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), dppb (0.08 mmol) or dppp (0.04 mmol), alkyne (2.0 mmol), thiol (2.0 mmol), *p*-TsOH (0.04 mmol), solvent (10 ml).

[b] Catalytic system: **A**: $Pd(OAc)_2$/ dppp/*p*-TsOH /THF/CO(300 psi)/110°C/6 h; **B**: $Pd(OAc)_2$/dppb/CO(300 psi)/H_2 (300 psi)/CH_2Cl_2/110°C/24 h.

[c] Isolated yields.

[d] The ratio **3**/**4** was determined by GC and ^1H NMR.

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15. Typical experimental procedure for the thiocarbonylation of alkynes with arylthiols: A mixture of 2.0 mmol of 1-heptyne **1b**, 2.0 mmol of thiophenol **2a**, 0.020 mmol of $Pd(OAc)_2$, and 0.08 mmol of dppb was dissolved in CH_2Cl_2 (10 ml) and placed in a 45 ml autoclave. The autoclave was purged, pressurized (600 psi of $CO+H_2$), and then heated (110°C). After 24 h, the reaction mixture was cooled to room temperature, filtered through Celite, and concentrated by rotary evaporation. Thioesters **3b** and **4b** were separated by preparative thin-layer chromatography using hexane–ethyl acetate (10:1) as solvent. All thioesters **3** and **4** were clearly identified and characterized by GC–MS, and ^1H and ^{13}C NMR spectroscopy.