Amide directed hydrocarboxylation of *N*-allylacetamide catalyzed by the aqueous Pd – tppts – Brønsted acid system (tppts = $P(C_6H_4$-*m*-$SO_3Na)_3$)[1]

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Abstract: The Pd – tppts – HOTs (tppts = $P(C_6H_4$-*m*-$SO_3Na)_3$, HOTs = *p*-toluenesulfonic acid) catalyzed hydrocarboxylation of *N*-allylacetamide in an aqueous medium afforded 4-acetamidobutyric acid and 3-acetamido-2-methylpropanoic acid under mild conditions, with a high regioselectivity towards the linear isomer. During the hydrocarboxylation an acid catalyzed hydrolysis of the amide moieties of both the substrate and the products took place, as well as the formation of acetamide and propanal, presumably via a Pd-catalyzed allylic substitution reaction of *N*-allylacetamide. The hydrolysis reaction was suppressed by lowering the amount of Brønsted acid cocatalyst (HOTs) or by employing a weaker Brønsted acid such as propanoic acid. The allylic substitution reaction was minimized by increasing the CO pressure but unfortunately this caused a decrease in the regioselectivity. A sudden inhibition took place after ca. 70% conversion, presumably caused by one of the side products. By increasing the tppts concentration to 13.1 mmol L^{-1} (20 equiv per Pd) the inhibition was circumvented and a quantitative conversion of *N*-allylacetamide was achieved.

Key words: aqueous media, olefins, palladium, hydrocarboxylation, *N*-allylacetamide.

Résumé : Le complexe Pd – tppts – HOTs (tppts = $P(C_6H_4$-*m*-$SO_3Na)_3$, HOTs = acide *p*-toluènesulfonique) catalyse l'hydrocarboxylation du *N*-allylacétamide, en solution aqueuse et dans des conditions douces, pour conduire à la formation des acides 4-acétamidobutyrique et 3-acétyl-2-méthylpropanoïque, avec une régiosélectivité élevée en faveur de l'isomère linéaire. Au cours de la réaction d'hydrocarboxylation, il se produit une hydrolyse acidocatalysée des portions amides tant du substrat que du produit ainsi que la formation d'acétamide et de propanal, probablement par le biais d'une réaction de substitution allylique du *N*-allylacétamide, catalysée par le Pd. La réaction d'hydrolyse peut être supprimée en abaissant la quantité de l'acide de Brønsted utilisé comme cocatalyseur (HOTs) ou en utilisant un acide de Brønsted plus faible, tel que l'acide propanoïque. On peut minimiser la réaction de substitution allylique en augmentant la pression de CO; toutefois, ceci provoque une diminution de la régiosélectivité. Après environ 70% de conversion, il se produit une inhibition soudaine de la réaction qui est probablement causée par l'un des produits secondaires. En augmentant la concentration de tppts jusqu'à une valeur de 13,1 mmol L^{-1} (20 équivalents par Pd), on peut prévenir l'inhibition et obtenir une conversion quantitative du *N*-allylacétamide.

Mots clés : milieu aqueux, oléfines, palladium, hydrocarboxylation, *N*-allylacétamide.

[Traduit par la Rédaction]

Introduction

Organometallic catalysis in aqueous media currently attracts much attention due to the advantages of using the safe, environmentally friendly and economically attractive process solvent: water (1). Recently, we and others have developed a novel aqueous biphasic system for the hydrocarboxylation of olefins (2). In the presence of a Brønsted acid cocatalyst consisting of weakly coordinating anions, the Pd–tppts catalyst efficiently converts partly water-soluble olefins, such as ethene, propene, or isobutene, into their corresponding hydrocarboxylation products: propionic acid, *n*- and isobutyric acid and 3-methylbutyric acid, respectively. Unfortunately, when higher olefins were applied, e.g., 1-octene, due to phase transfer limitations, the reaction rate decreased dramatically, accompanied by the decomposition of the catalyst.

We have also shown that a hetero-atom substituted olefin, *N*-allylacetamide, was smoothly converted into 4-acetamidobutanal and 3-acetamido-2-methylpropanal by a Rh–tppts catalyzed hydroformylation reaction in water (3). In comparison with the conventional Rh–PPh_3 catalyst in an

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Dedicated to Professor Brian R. James on the occasion of his 65th birthday.

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Scheme 1. The hydrocarboxylation of *N*-allylacetamide.

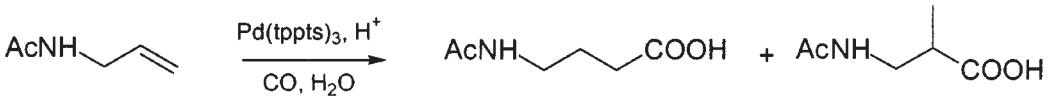


Table 1. The Pd–tppts catalyzed hydrocarboxylation of *N*-allylacetamide.

Experiment[a]	Temperature (°C)	Pressure (bar)	Time (h)	Yield (%)		1:b Ratio	Allylic substitution (%)[b]	Hydrolysis (%)[c]
				n	iso			
1/1	80	10	2	21.2	0.7	29.1	7.7	0
			8	27.8	1.7	16.0	8.0	1.7
1/2	60	10	8	30.3	2.1	14.6	9.6	0
			24	41.5	3.3	12.5	12.8	1.3
1/3	40	10	8	4.0	0.3	11.5	2.9	0
			24	14.9	1.1	13.6	7.4	0
1/4[d]	60	10	8	37.3	2.8	13.4	14.0	0
			24	41.6	3.7	11.4	14.4	11.6
1/5[d]	60	30	8	38.8	5.8	6.7	9.2	3.5
			24	44.1	8.3	5.3	12.1	10.5
1/6[d]	60	50	8	38.4	8.5	4.5	8.9	2.9
			24	43.6	11.5	3.8	9.5	9.0

[a]Reaction conditions: 50 μmol $PdCl_2$, 0.50 mmol tppts, 0.50 mmol *p*-toluenesulfonic acid, 10.0 mmol *N*-allylacetamide, 2.0 mmol *n*-BuOH (internal standard), 76.5 g total amount of reaction mixture.
[b]Both propanal and acetamide, were formed in equal amounts.
[c]Calculated from the amount of HOAc formed.
[d]2.50 mmol *p*-toluenesulfonic acid.

organic solvent, e.g., toluene or THF, the reaction in water proceeded considerably faster and in a higher selectivity towards the aldehydes. The rapid hydroformylation of *N*-allylacetamide in water suggested that the Pd–tppts catalyzed hydrocarboxylation reaction of this water-soluble olefin, affording 4-acetamidobutyric acid and 3-acetamido-2-methylpropanoic acid (Scheme 1), might proceed smoothly in a neat aqueous medium as well. The de-acetylated derivative of the linear product, γ-aminobutyric acid (GABA), is a well-known neurotransmitter with interesting pharmacological properties.

The hydrocarboxylation and alkoxycarbonylation of amide-functionalized olefins have been sporadically reported. Becker et al. (4) described the $PdCl_2(PPh_3)_2$ catalyzed methoxycarbonylation of *N*-vinylphtalimide in 2-butanone. After a 21 h reaction time at 70°C and 100 bar CO pressure, in the presence of 1% catalyst, 48% of the olefin was converted into the methylester of 2-phthalimidopropanoic acid. Ojima and Zhang (5) reported the methoxycarbonylation of *N*-allylbenzamide in the presence of $PdCl_2(PPh_3)_2$ in benzene at 80°C and a CO pressure of 100 bar. The products methyl-4-benzamidobutanoate and methyl-3-methyl-3-benzamidopropanoate were obtained in 18% and 71% yield, respectively. Magnus and Slater (6) studied the $Co_2(CO)_8$ catalyzed carbonylation of *N*-allylacetamide in ethylacetate, in the presence of 1 equiv of water. Under forcing conditions (140–160°C), a mixture of 2-acetamidobutyric acid and 2-acetamido-2-methylpropanoic acid was obtained in a 3.8:1 ratio. The formation of the linear hydrocarboxylation product 4-acetamidobutyric acid was not observed. When a combination of Co and Rh carbonyl precursors was used, the selectivity increased towards 2-acetamidobutyric acid.

In this paper we report on the hydrocarboxylation of *N*-allylacetamide in water catalyzed by the Pd – tppts – Brønsted acid system. The high water-solubility of *N*-allylacetamide enabled us to study this reaction in a single phase aqueous medium, i.e., in the absence of phase transfer limitations.

Results and discussion

In the hydrocarboxylation experiments we started with a freshly prepared catalyst solution by codissolving $PdCl_2$ and 10 equiv of tppts in water. We previously observed by NMR that under these conditions a cationic $[PdCl(tppts)_3]^+$ intermediate is formed, which is rapidly reduced to $[Pd(tppts)_3]$ in the presence of CO (7). We assume that this reduction is complete before the autoclave has reached the reaction temperature (within 8 min). We have also established by multinuclear NMR experiments, that $[Pd(tppts)_3]$ is protonated by the acid cocatalyst to afford the cationic $[PdH(tppts)_3]^+$, which reacts with ethene and CO to give a relatively stable Pd–acyl intermediate (8). The rate determining hydrolysis of the Pd—acyl bond affords propanoic acid and the Pd–hydride which returns to the catalytic cycle. Since we did not observe any induction period in our hydrocarboxylation reactions, we assume that the generation of the active catalyst is complete when the reaction temperature was reached.

When the hydrocarboxylation of *N*-allylacetamide was carried out under similar reaction conditions to those which we previously applied for ethene and propene (110°C, 50 bar) (2*a*), severe catalyst decomposition took place. In contrast, at a reaction temperature below 80°C the catalyst remained

Table 2. The Pd – tppts – Brønsted acid catalyzed hydrocarboxylation of *N*-allylacetamide.

Experiment[a]	Brønsted acid (mmol)	Time (h)	Yield (%)		1:b Ratio	Allylic substitutuion (%)	Hydrolysis (%)
			n	iso			
2/1	HOTs (0.5)	8	30.3	2.1	14.6	9.6	0
		24	41.5	3.3	12.5	12.8	1.3
2/2	HOTs (2.5)	8	37.3	2.8	13.4	14.0	0
		24	41.6	3.7	11.4	14.4	11.6
2/3	HOTs (5.0)	8	37.0	2.8	13.3	11.1	7.9
		24	35.3	3.8	9.2	11.4	21.2
2/4	HCl (2.5)	8	27.9	2.3	12.4	8.1	3.1
		24	38.6	4.8	8.0	11.1	10.8
2/5	$HOOCCH_2CH_3$ (2.5)	8	26.4	2.0	13.0	11.6	0
		24	36.9	3.2	11.4	14.7	1.6

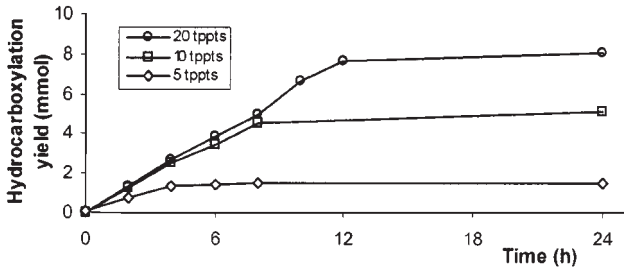
[a]Reaction conditions: see Table 1; 60°C, 10 bar CO.

Table 3. The Pd – tppts – Brønsted acid catalyzed hydrocarboxylation of *N*-allylacetamide.

Experiment[a]	Tppts–Pd	Time (h)	Yield (%)		1:b Ratio	Allylic substitution (%)	Hydrolysis (%)
			n	iso			
3/1[b]	5	8	12.5	1.2	10.8	4.3	2.8
		24	12.3	1.7	7.2	5.1	5.3
	Extra tppts	60	55.9	4.8	11.6	22.9	15.4
3/2	10	8	37.3	2.8	13.4	14.0	0
		24	41.6	3.7	11.4	14.4	11.6
3/3	20	8	44.0	2.7	16.1	14.1	3.4
		12	61.7	3.6	17.2	21.0	5.4
		24	61.4	4.0	15.9	21.3	10.6

[a]Reaction conditions: see Table 1; 2.50 mmol *p*-toluenesulfonic acid, 60°C, 10 bar CO.
[b]10 equiv of tppts added at t = 24 h.

Fig. 1. The effect of the tppts concentration on the progress of the reaction (reaction conditions: see Table 3).

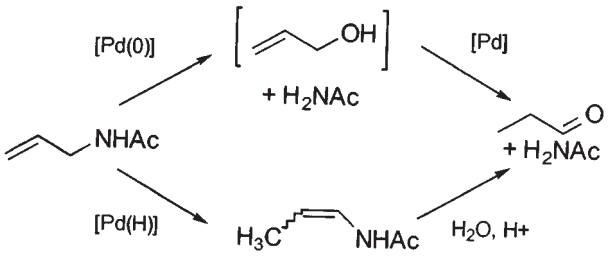


intact and converted *N*-allylacetamide into 4-acetamidobutyric acid and 3-acetamido-2-methylpropanoic acid (Table 1). During the reaction some acetic acid was formed via an acid-catalyzed hydrolysis of the amide moieties in *N*-allylacetamide and both carboxylic acid products. Decreasing the amount of HOTs to 0.50 mmol led to a slower hydrolysis (1.3% after 24 h reaction time (Table 2, Experiment 2/1)) with only a small compromise in the initial hydrocarboxylation rate. The hydrolysis reaction was also suppressed by using a much weaker Brønsted acid cocatalyst (we chose propionic acid for analysis reasons).

In addition to hydrocarboxylation and hydrolysis products we also observed the formation of acetamide, propanal, and traces of allylalcohol. The formation of these side products continues at room temperature, in the absence of CO, which necessitated immediate analysis of the samples (within 5 min) as soon as they were withdrawn from the reaction mixture. The formation of acetamide and propanal could be suppressed to some extent by increasing the CO pressure, but unfortunately, this also resulted in a considerably lower regioselectivity (1:b = 4 at 50 bar CO, Experiment 1/6). We suggest that a Pd-catalyzed allylic substitution reaction of *N*-allylacetamide takes place, affording acetamide and allylalcohol, of which the latter is isomerized to propanal (Scheme 2). In basic media, such an allylic hydrolysis reaction occurs readily at room temperature (9). The reaction apparently also proceeds under our mildly acidic conditions. Alternatively, *N*-allylacetamide might undergo an isomerization reaction to 1-acetamidopropene, followed by a fast acid-catalyzed hydrolysis, which would also afford acetamide and propanal. However, the absence of 1-acetamidopropene in the reaction mixtures and the high stability of the related enamide, *N*-methyl-*N*-vinylacetamide, under representative reaction conditions are not consistent with the latter explanation and, thus, would favour the allylic substitution mechanism.

The much higher regioselectivity towards the linear carboxylic acid in the hydrocarboxylation of *N*-allylacetamide, compared to propene (1:b = 1.3–1.6, irrespective of the conditions applied) suggests that the amide moiety has a directing effect. During the insertion of the C=C bond into the Pd—hydride bond, at which stage the regioselectivity is determined, the amide might coordinate to the palladium. We envisage two possible mechanisms that explain the higher selectivity to the linear isomer compared to the hydrocarboxylation of the nonfunctionalized olefin

Scheme 2. Possible mechanisms for the formation of propanal and acetamide.



propene (Scheme 3): (*i*) coordination takes place via the nitrogen which favours the formation of the anti-Markovnikov addition product (1) while there is not a large difference in reactivity of both Pd–alkyl intermediates (**1** and **2**) towards CO; (*ii*) coordination takes place via the oxygen; Markovnikov addition of Pd-H to *N*-allylacetamide affords the six-membered chelate (**4**), which is more stable but less reactive towards CO compared to the anti-Markovnikov addition product (**3**).

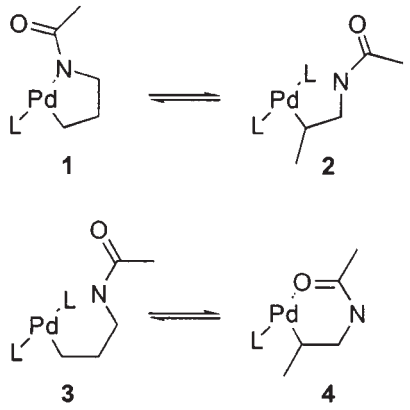
The experiments in Tables 1 and 2 reveal that the 1:b ratio decreases at higher pressures, indicating that the amide moiety competes with CO for coordination to the palladium. The rate of hydrocarboxylation is, however, independent of the pressure, which suggests that the first mechanism is operative, since a higher reactivity at higher pressures would be expected if inhibition is due to the formation of a putative stable intermediate such as **4**.

In all experiments reported in Tables 1 and 2, conducted at 60°C, the reaction rates remained constant up to ca. 70% conversion, after which inhibition was observed. Although the catalyst decomposes at temperatures >80°C, at 60°C we did not observe a black precipitate, indicating that this sudden decrease in reaction rate is not due to decomposition of the catalyst. Neither the Brønsted acid concentration, the type of Brønsted acid, the pressure, nor temperature had a significant effect on the inhibition. Addition of extra *N*-allylacetamide at t = 24 h also gave no further reaction, which rules out a possible need for a threshold substrate concentration. Only by increasing the concentration of the ligand to 13.1 mmol L^{-1} (20 equiv per Pd) were we able to achieve full conversion. In the absence of tppts the catalyst decomposed, while when 5 equiv of phosphine were added, the reaction was already inhibited after 24% conversion. Addition of more tppts as a solid to the latter reaction mixture (Experiment 3/1) led to an almost quantitative conversion.

As previously shown by a number of groups, tppts reacts with unsaturated compounds, such as acrylic acid esters, unsaturated alcohols and aldehydes, in the presence of an acid, to afford phosphonium salts (10). However, under our reaction conditions (60°C, [tppts] = 6.5 mmol L^{-1}, [*N*-allylacetamide] = 0.13 mol L^{-1}, [HOTs] = 6.5 mmol L^{-1}) the tppts ligand remained unchanged; no formation of phosphonium salts from tppts, *N*-allylacetamide, and HOTs or phosphine oxide was observed by ^{31}P NMR spectrometry. We assume that the observed inhibition of the hydrocarboxylation is caused by the coordination of byproducts that can only be displaced by an excess of tppts.

By adding 4-acetamidobutyric acid and 3-acetamido-2-methylpropanoic acid to the reaction mixture at the beginning of the experiment, we again observed an inhibition after ca. 70% conversion, just as in the case of the previously described experiments. We conclude that not the hydrocarboxylation products, but one (or more) of the side products formed in the competing hydrolysis and allylic substitution reaction, are responsible for the lower reaction rate. Further studies should reveal the identity of the actual inhibitor.

Scheme 3. Possible intermediates in the hydrocarboxylation of *N*-allylacetamide.



Finally, we observed that during the hydrocarboxylation reaction the 1:b ratio decreases with time. Since the rate of hydrolysis of both carboxylic acid products is similar, the decrease in regioselectivity must be due to changes in the coordination sphere of the palladium. We suggest that a coordinating compound can alter the coordination sphere in such a manner that the amide substituent of allylacetamide can no longer fulfil its directing effect during the insertion of the C=C bond into the Pd—hydride bond (Scheme 2). This phenomenon is also the subject of further investigations.

Experimental details

All manipulations were done under an nitrogen atmosphere. Tppts (11), *N*-allylacetamide (12), *N*-acetyl-4-aminobutyric acid, and *N*-acetyl-3-amino-2-methylpropanoic acid (13) were prepared according to previously described procedures. All other chemicals are commercially available. HPLC analyses were done using a Phenomenex organic acid collumn using a solution of 0.01 M trifluoroacetic acid in water as eluent.

Hydrocarboxylation reactions

Tppts and $PdCl_2$ were codissolved in water and the resulting bright yellow solution was transferred into a 300 mL Hasteloy C Parr autoclave that contains an aqueous solution of the Brønsted acid, the substrate, and *n*-BuOH (standard). The autoclave was closed, the nitrogen atmosphere was replaced by CO, and the autoclave was heated. When the contents reached reaction temperature (t = 0) samples were taken at regular time intervals (t = 0. 2, 4, 6, 8, and 24 h). The samples were analyzed by HPLC immediately (within 5 min). The products were identified by LC–MS and by comparing the ^{1}H and ^{13}C NMR spectra and the retention times with those of the authentic samples.

Conclusions

In comparison with the Rh–tppts catalyzed hydroformylation, the Pd–tppts catalyzed hydrocarboxylation of *N*-allylacetamide in water proceeds considerably less facile. Nevertheless, in comparison with related Pd chemistry in organic media, the results obtained are encouraging. The hydrocarboxylation of *N*-allylacetamide proceeds with a high regioselectivity towards 4-acetamidobutyric acid under mild reaction conditions, but the reaction is complicated by the hydrolysis of amide moieties in the substrate and the products, a competing allylic substitution reaction and a sudden inhibition, caused by side products. Amide hydrolysis was suppressed by optimization of the concentration of the Brønsted acid cocatalyst and the formation of acetamide and propanal was minimized by increasing the CO pressure. Unfortunately a higher CO pressure led to a lower regioselectivity. The inhibition could be circumvented by increasing the concentration of the ligand.

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References

1. (*a*) B. Cornils and W.A. Herrmann (*Editors*). Aqueous-phase organometallic catalysis. Wiley–VCH, Weinheim, Germany. 1998; (*b*) G. Verspui, G.J. ten Brink, and R.A. Sheldon. Chemtracts: Org. Chem., **12**, 777 (1999)
2. (*a*) G. Verspui, J. Feiken, G. Papadogianakis, and R.A Sheldon. J. Mol. Catal. A: Chem. **146**, 299 (1999); (*b*) G. Papadogianakis, G. Verspui, L. Maat, and R.A. Sheldon. Catal. Lett. **47**, 43 (1997); (*c*) B. Xie, Y. Kou, and Y.Ying. Fenzi Cuihua, **11**, 81 (1997); (*d*) S. Tilloy, E. Monflier, F. Bertoux, Y. Castanet, and A. Mortreux. New J. Chem. **21**, 529 (1997); (*e*) F. Bertoux, S. Tilloy, E. Monflier, Y. Castanet, and A. Mortreux. J. Mol Catal. A: Chem. **138**, 53 (1999).
3. G. Verspui, G. Elbertse, F.A. Sheldon, M.A.P.J. Hacking, and R.A. Sheldon. Chem. Commun. 1363 (2000).
4. Y. Becker, A. Eisenstadt, and J.K. Stille. J. Org. Chem. **45**, 2145 (1980).
5. I. Ojima and Z. Zhang. J. Org. Chem. **53**, 4422 (1988).
6. P. Magnus and M. Slater. Tetrahedron Lett. **28**, 2829 (1987).
7. G. Papadogianakis, J.A. Peters, L. Maat, and R.A. Sheldon. Chem. Commun. 1105 (1995).
8. G. Verspui, I.I. Moiseev, and R.A. Sheldon. J. Organomet. Chem. **586**, 196 (1999).
9. (*a*) J.P. Genêt, E. Blart, M. Savignac, J.M. Paris, and J.M. Bernard. Tetrahedron Lett. **34**, 4189 (1993); (*b*) S. Lemaire-Audoire, M. Savignac, E. Blart, G. Pourcelot, J.P. Genêt, and J.M. Bernard. Tetrahedron Lett. **35**, 8783 (1994); (*c*) J.P. Genêt, E. Blart, M. Savignac, S. Lemeune, S. Lemaire-Audoire, J.M. Paris, and J.M. Bernard. Tetrahedron, **50**, 497 (1994); (*d*) S. Lemaire-Audoire, M. Savignac, G. Pourcelot, J.P. Genêt, and J.M. Bernard. J. Mol. Catal. A: Chem. **116**, 247 (1997).
10. (*a*) C. Larpent and H. Patin. Tetrahedron Lett. **29**, 4577 (1988); (*b*) C. Larpent and H. Patin. Tetrahedron, **44**, 6107 (1988); (*c*) C. Larpent, G. Meignan, J. Priol, and H. Patin. C.R. Acad. Sci. Ser. II: 493 (1990); (*d*) D.J. Darensbourg, F. Joó, A. Kathó, J.N. White Stafford, A. Bényei, and J.H. Reibenspies. Inorg. Chem. **33**, 175 (1994); (*e*) M. Hernandez and P. Kalck. J. Mol. Catal. A: Chem. **116**, 131 (1997).
11. W.A. Herrmann and C.W. Kohlpaintner. Inorg. Synth. **32**, 8 (1998).
12. G. Schlegel and H.J. Schaefer. Chem. Ber. **117**, 1400 (1984).
13. A. Mori. J. Biochemistry, **46**, 60 (1959).