ORGANIC LETTERS

2003
Vol. 5, No. 18
3241−3244

Palladium-Catalyzed, Carboxylic Acid-Assisted Allylic Substitution of Carbon Nucleophiles with Allyl Alcohols as Allylating Agents in Water

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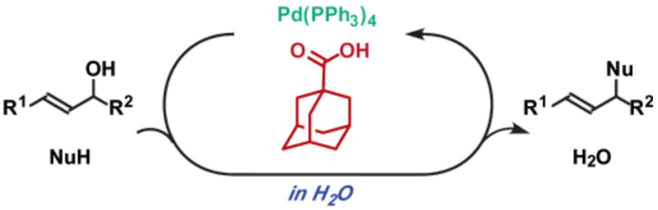
Received June 18, 2003

ABSTRACT



Allylic substitution of allyl alcohols in water as a suspension medium has been realized using a combination of tetrakis(triphenylphosphine)-palladium and a carboxylic acid such as 1-adamantanecarboxylic acid. Various substrates turned out to be applicable to this catalytic system.

Palladium-catalyzed allylic substitution with carbon nucleophiles constitutes one of the most important and useful carbon−carbon bond-forming reactions in organic synthesis.[1] In most cases, allyl esters (usually with a stoichiometric amount of a base) or allyl carbonates, which are usually prepared from the corresponding allyl alcohols, have been used as allylating agents. Therefore, if allyl alcohols themselves can be directly used as allylating agents, the steps to prepare the esters or carbonates are no longer needed and the overall process of the allylation would become highly efficient and atom economical. Since this type of allylic substitution is rather slow, some efforts have been made to accelerate the palladium-catalyzed reactions.[2] In many cases, however, stoichiometric amounts of activating agents such as Lewis acids are used.[3] Although there are several examples of allylic substitution using catalytic amounts of activating agents,[4] further exploration of this atom-economical carbon−carbon bond formation is still needed.

Organic reactions in water have recently attracted much attention, not only because unique reactivity is often observed in water but also because water is a safe and economical substitute for conventional organic solvents.[5] Thus, development of atom-economical reactions in water is one of the most important goals of synthetic chemistry. Here we disclose a new catalytic system for palladium-catalyzed

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[1] (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1995. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

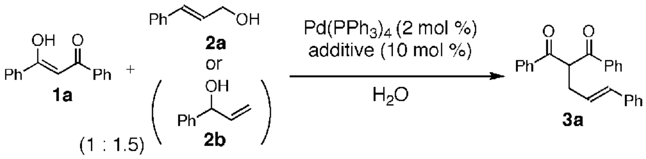
[2] (a) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, *11*, 3821. (b) Haudegond, J.-P.; Chauvin, Y.; Commereuc, D. *J. Org. Chem.* **1979**, *44*, 3063. (c) Bergbreiter, D. E.; Weatherford, D. A. *J. Chem. Soc., Chem. Commun.* **1989**, 883. (d) Bergbreiter, D. E.; Weatherford, D. A. *J. Org. Chem.* **1989**, *54*, 2726. (e) Shimizu, I.; Toyoda, M.; Terashima, T.; Oshima, M.; Hasegawa, H. *Synlett* **1992**, 301. (f) Sakakibara, M.; Ogawa, A. *Tetrahedron Lett.* **1994**, *35*, 8013. (g) Bricout, H.; Carpentier, J.-F.; Mortreux, A. *J. Mol. Catal. A: Chem.* **1998**, *136*, 243.

[3] (a) Lu, X.; Jiang, X.; Tao, X. *J. Organomet. Chem.* **1988**, *344*, 109. (b) Itoh, K.; Hamaguchi, N.; Miura, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2833. (c) Stary, I.; Stará, I. G.; Kocovsky, P. *Tetrahedron* **1994**, *50*, 529. (d) Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1065. (e) Tamaru, Y.; Horino, Y.; Araki, M.; Tanaka, S.; Kimura, M. *Tetrahedron Lett.* **2000**, *41*, 5705. (f) Horino, Y.; Naito, M.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2001**, *42*, 3113. (g) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401.

[4] (a) Lu, X.; Lu, L.; Sun, J. *J. Mol. Catal.: Chem.* **1987**, *41*, 245. (b) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968.

10.1021/ol035126q CCC: $25.00

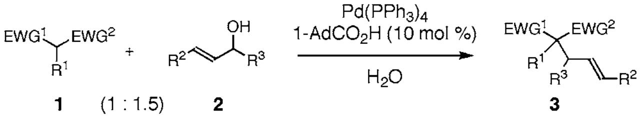
Table 1. Effect of Additives on Palladium-Catalyzed Allylic Substitution

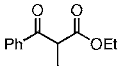
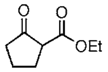
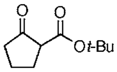
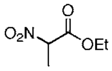
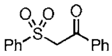
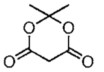
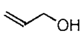
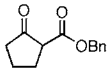
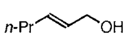
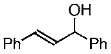


entry	additive	conditions	yield (%)[a]
1	–	70 °C, 30 min	1
2	$CH_3(CH_2)_{10}CO_2H$	70 °C, 30 min	28
3[b]	$CH_3(CH_2)_{10}CO_2H$	70 °C, 30 min	0
4	$PhCO_2H$	70 °C, 30 min	13
5	CH_3CO_2H	70 °C, 30 min	12
6	4-Oct$C_6H_4CO_2H$	70 °C, 30 min	10
7	Ph_2CHCO_2H	70 °C, 30 min	4
8	$PhOCH_2CO_2H$	70 °C, 30 min	2
9	1-AdCO_2H	70 °C, 30 min	30
10	C_6F_5OH	70 °C, 30 min	6
11	HCl	reflux, 30 min	13
12	DBSA	reflux, 30 min	7
13	–	reflux, 30 min	39
14	$CH_3(CH_2)_{10}CO_2H$	reflux, 15 min	93 (86)[c]
15	1-AdCO_2H	reflux, 15 min	98 (87)[c]
16[d]	1-AdCO_2H	reflux, 15 min	81
17[e]	1-AdCO_2H	reflux, 15 min	92
18[f]	1-AdCO_2H	reflux, 15 min	89
19[g]	–	reflux, 30 min	6
20[g]	$CH_3(CH_2)_{10}CO_2H$	reflux, 30 min	1
21[h]	–	reflux, 30 min	2
22[h]	$CH_3(CH_2)_{10}CO_2H$	reflux, 30 min	3

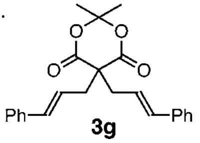
[a] NMR yield. [b] Without $Pd(PPh_3)_4$. [c] Isolated yield. [d] $Pd(OAc)_2$ (2 mol %) and PPh_3 (10 mol %) were used instead of $Pd(PPh_3)_4$. [e] **1a**:**2a** = 1:1. [f] **2b** was used instead of **2a**. [g] In toluene. [h] In 1,4-dioxane.

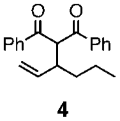
Table 2. Allylic Substitution of Various Substrates



entry	1	2	$Pd(PPh_3)_4$ (mol %)	conditions	product	yield[a] (%)
1	 **1b**	**2a**	5	reflux, 5 h	**3b**	90
2	 **1c**	**2a**	2	reflux, 10 min	**3c**	92
3	 **1d**	**2a**	2	reflux, 10 min	**3d**	76
4	 **1e**	**2a**	5	reflux, 1 h	**3e**	78
5[b]	 **1f**	**2a**	2	80 °C, 1.5 h	**3f**	>99
6[c]	 **1g**	**2a**	0.5	80 °C, 30 min	**3g**	74[d]
7	**1a**	 **2c**	5	80 °C, 30 min	**3h**	73
8	 **1h**	**2c**	5	80 °C, 20 min	**3i**	93
9	**1a**	 **2d**	5	80 °C, 2 h	**3j**	80[e]
10[b]	**1a**	 **2e**	5	reflux, 30 min	**3k**	88

[a] Isolated yield. [b] Molar ratio of **1**:**2** is 1:1.1. [c] Molar ratio of **1**:**2** is 1:2.2. [d] Product was diallylated compound **3g**. [e] Containing regioisomer **4** (4% yield).


3g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allylic substitution of allyl alcohols with carbon nucleophiles in water as a suspension medium.[6] The key of the catalytic system is the use of a catalytic amount of a carboxylic acid, which greatly accelerates the reactions.[7]

At first, we carried out the reaction of compound **1a** with cinnamyl alcohol **2a** in the presence of $Pd(PPh_3)_4$ as a catalyst and a large excess of water. The reaction hardly proceeded, and the desired product **3a** was obtained in only 1% yield (Table 1, entry 1). To our surprise, however, use of a catalytic amount (10 mol %) of lauric acid as an additive greatly improved the yield to 28% (entry 2). This increase of the reactivity can be attributed to cooperative effects of both the palladium catalyst and lauric acid, because lauric acid alone did not give **3a** at all (entry 3). We also tested other carboxylic acids and found that 1-adamantanecarboxylic acid (1-AdCO_2H) was as effective as lauric acid (entry 9). Strong acids such as HCl and dodecylbenzenesulfonic acid (DBSA)[8] retarded the substitution reaction (entries 11 and 12 vs 13). When the reaction was performed under reflux conditions in the presence of lauric acid or 1-AdCO_2H, a reaction time of 15 min was sufficient to give **3a** in high yields (entries 14 and 15). It is noted that this dehydration, which affords water as a coproduct, proceeds even in the presence of a large excess of water. A combination of palladium acetate with PPh_3 was also effective (entry 16). Use of 1 equiv of **2a** turned out to be sufficient to give the product in high yield (entry 17). In addition, use of isomeric allyl alcohol **2b** instead of **2a** gave the same product **3a** in high yield (entry 18). It is also noteworthy that, in toluene or 1,4-

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(5) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (c) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (d) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4095.

(6) For palladium-catalyzed allylic substitution in water, see: (a) Bergbreiter, D. E.; Liu, Y.-S. *Tetrahedron Lett.* **1997**, *38*, 7843. (b) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 3557. (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8303. (d) Danjo, H.; Tanaka, D.; Hayashi, T.; Uozumi, Y. *Tetrahedron* **1999,** *55*, 14341. (e) Kobayashi, S.; Lam, W. W.-L.; Manabe, K. *Tetrahedron Lett.* **2000**, *41*, 6115. (f) Rabeyrin, C.; Nguefack, C.; Sinou, D. *Tetrahedron Lett.* **2000**, *41*, 7461. (g) Hashizume, T.; Yonehara, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2000**, *65*, 5197. Palladium-catalyzed allylic amination of 1,1-dimethylallyl alcohol in water was observed: (h) Yokoyama, Y.; Hikawa, H.; Mitsuhashi, M.; Uyama, A.; Murakami, Y. *Tetrahedron Lett.* **1999**, *40*, 7803.

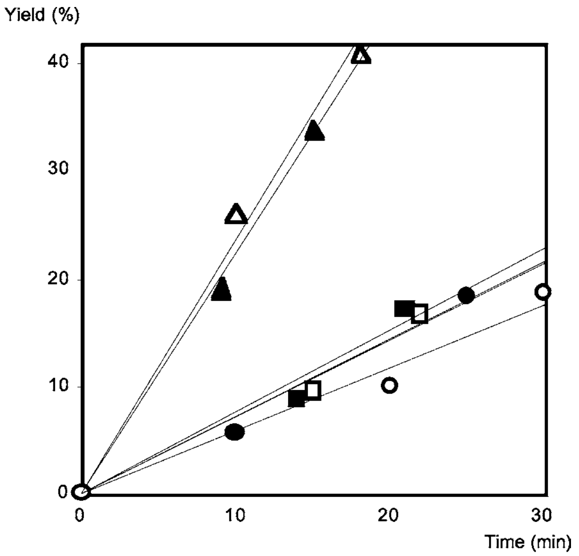


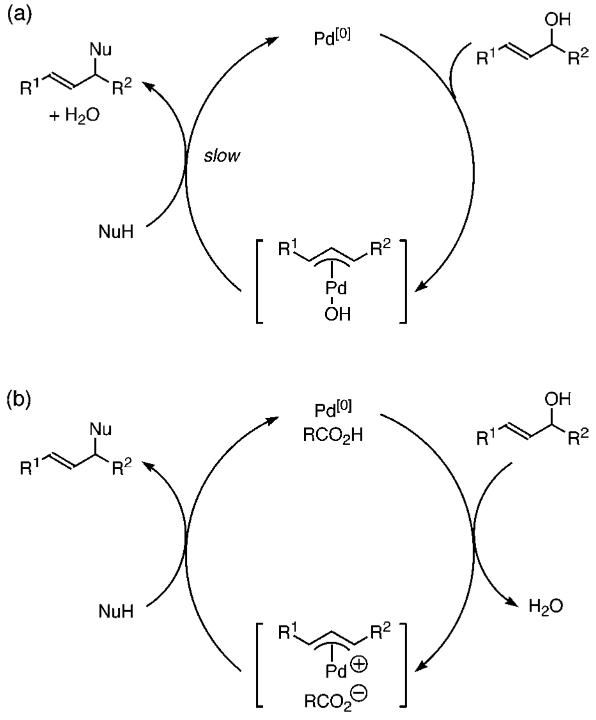
Figure 1. Plot of yield vs time for allylic substitution without 1-AdCO$_2$H in water. Conditions: Pd(PPh$_3$)$_4$ (2 mol %), **1**:**2** = 1:1.5, at 100 °C in water. The yields were determined by ^{1}H NMR. Open circle, **1a** + **2a**; open square, **1b** + **2a**; open triangle, **1f** + **2a**; closed circle, **1a** + **2b**; closed square, **1b** + **2b**; closed triangle, **1f** + **2b**.

dioxane, the reaction was very slow and the dramatic effect of the carboxylic acid additive was not observed (entries 19–22).

Next, we applied the combination of Pd(PPh$_3$)$_4$ and 1-AdCO$_2$H to other substrates as shown in Table 2. Various pronucleophiles having two electron-withdrawing groups (EWG) were found to react, and the corresponding products were obtained in high yields. In the cases of **1a** and **1f**, the corresponding monoallylated products were selectively obtained in high yields (Table 1, entry 15, and Table 2, entry 5). In the case of **1g**, however, the second allylation easily occurred, and when 2.2 equiv of **2a** was used, the bis-allylated product was obtained in good yield (entry 6). As for allyl alcohols, not only cinnamyl alcohol but also allyl alcohol **2c**, alkyl-substituted alcohol **2d**, and 1,3-disubstituted alcohol **2e** were successfully used.

Although the reaction mechanism of the present catalytic system has not yet been fully elucidated, the kinetic studies mentioned below suggested the role of the carboxylic acid. Figure 1 shows plots of yield vs time for the palladium-catalyzed reactions of pronucleophiles (**1a**, **1b**, or **1f**) with allyl alcohols (**2a** or **2b**) in the absence of an additive in water at 100 °C. From the plots, it is clear that **2a** and **2b** exhibited almost identical reactivities for each pronucleophile. It is unlikely that **2b** is rapidly isomerized to thermodynamically more stable **2a** before the reaction with a nucleophile, because heating of a 1.5:0.02 mixture of **2b** and Pd(PPh$_3$)$_4$ in water under reflux conditions for 30 min gave only 3% of **2a**, accompanied by 84% of **2b**. Thus, the almost identical reactivities of **2a** and **2b** are in accord with the mechanism in which they are converted to the same intermediate, the corresponding π-allylpalladium. In addition, it was also found from Figure 1 that the rates of the reactions depend on the pronucleophiles used (the order of the reactivity was **1f** > **1a** ≈ **1b**). From these results, we assume a mechanism where the pronucleophiles (or their deprotonated forms) are involved in the rate-determining step as shown in Scheme 1(a) (NuH = pronucleophile, PPh$_3$ is omitted for clarity).

Scheme 1. Possible Catalytic Cycle of the Allylic Substitution of Allyl Alcohols



On the other hand, the results of the palladium-catalyzed reactions in the presence of a carboxylic acid were found to be less clear. Figure 2 shows the plots of yield vs time in the presence of 1-AdCO$_2$H at 70 °C. Although the reactivity order of the pronucleophiles (**1f** > **1a** > **1b**) is different from that without 1-AdCO$_2$H, the rates of the reactions depend on the pronucleophiles used, indicating again that they are involved in the rate-determining step. Contrary to the case without 1-AdCO$_2$H, however, the rates also depend on the allyl alcohols used. Alcohol **2b** shows slightly higher reactivity than **2a**.[9] While it is difficult to explain this behavior at this stage, we propose a catalytic cycle in the

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(7) For examples of the use of Pd catalysts with carboxylic acids, see: (a) Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161. (b) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262.

(8) DBSA has been successfully used for acid-catalyzed reactions in water: (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537. (b) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971.

(9) This behavior was also observed at 100 °C. See Supporting Information. The reaction of **1a** with **2b** in the presence of 10 mol % 1-AdCO$_2$H in water at 70 °C for 10 min without the palladium catalyst gave only a trace amount of **3a**. This result indicates that the existence of another, acid-catalyzed pathway in the case of **2b** is not likely.

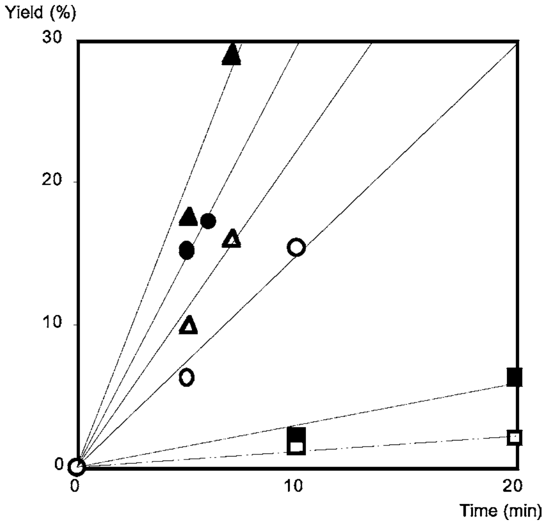

Figure 2. Plot of yield vs time for allylic substitution in the presence of 1-$AdCO_2H$ in water. Conditions: $Pd(PPh_3)_4$ (2 mol %), 1-$AdCO_2H$ (10 mol %), **1**:**2** = 1:1.5, at 70 °C in water. The yields were determined by ^1H NMR. Open circle, **1a** + **2a**; open square, **1b** + **2a**; open triangle, **1f** + **2a**; closed circle, **1a** + **2b**; closed square, **1b** + **2b**; closed triangle, **1f** + **2b**.

presence of the carboxylic acid as shown in Scheme 1b, considering the rate-determining step in the absence of the acid. The main role of the acid would be acceleration of the slow process after the π-allylpalladium formation.[10] Formation of a cationic π-allylpalladium[11] with the carboxylate counteranion could be the key for the rate enhancement by the acid.[12] On the other hand, the carboxylate anion should also be sufficiently basic to deprotonate a pronucleophile.[13] As shown in Table 1, DBSA, which is more acidic than the carboxylic acids, was not effective as an additive. This result can be explained by considering the weaker basicity of the corresponding sulfonate anion, which should be produced on the formation of the π-allylpalladium. Although we do not have clear experimental results to explain the rate differences between **2a** and **2b** at this stage, such a discrepancy may be attributed to differences in the properties of alcohols such as polarity, which might affect the acceleration effect of the carboxylic acid in a concentrated organic phase suspended in water. In any event, while the mechanism in Scheme 1 may be oversimplified, it presents the unique role of a catalytic amount of a carboxylic acid in palladium-catalyzed allylic substitution.

In conclusion, we have developed a catalytic system that enables reactions of carbon nucleophiles with allyl alcohols as allylating agents in water. Neither allyl esters with stoichiometric amounts of bases nor allyl carbonates are required. Furthermore, organic solvents are not needed for the reactions to proceed. Although catalytic reactions in water have attracted considerable attention, many catalytic systems that are effective in dry organic solvents often fail to work in water. Thus, proper modifications of the catalytic systems are essential to developing efficient systems that work well in water. In the present catalytic system, the key is the use of a carboxylic acid such as 1-$AdCO_2H$, which accelerates the palladium-catalyzed allylic substitution. It is noteworthy that the addition of a catalytic amount of a simple carboxylic acid dramatically enhances the rate of the reactions and that this effect of the acid was not observed in organic solvents. While the present catalytic reactions remain to be improved further, they will lead to a system that reduces the use of expensive or toxic organic solvents and stoichiometric amounts of activating agents. Further investigation on asymmetric allylic substitution is now in progress.

Acknowledgment. This work was partially supported by CREST and SORST, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Science.

Supporting Information Available: Experimental section and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] The formation of the π-allylpalladium may be also accelerated by the acid, possibly by protonation to increase the leaving group ability of the OH group of the allyl alcohol: Xiao, W.-J.; Alper, H. *J. Org. Chem.* **1998**, *63*, 7939. Acid-catalyzed (self-catalyzed) ester formation between the carboxylic acid with the allyl alcohol prior to the π-allylpalladium formation is unlikely, because heating a 1:1 mixture of **2a** and 1-$AdCO_2H$ in water under reflux conditions for 10 min gave only a trace amount of the corresponding ester, indicating that the ester formation was much slower than the allylic substitution. For the equilibrium positions of ester formation of hydrophobic substrates in water, see ref 7b.

[11] Amatore, C.; Jutand, A.; Meyer, G.; Mottier, L. *Chem. Eur. J.* **1999**, *5*, 466.

[12] In rhodium-catalyzed cross coupling of allyl alcohols with boronic acids, Kabalka et al. discussed the effect of a stoichiometric amount of HF as an additive in a similar manner: Kabalka, G. W.; Dong, G.; Venkataiah, B. *Org. Lett.* **2003**, *5*, 893.

[13] Giambastiani, G.; Poli, G. *J. Org. Chem.* **1998**, *63*, 9608.