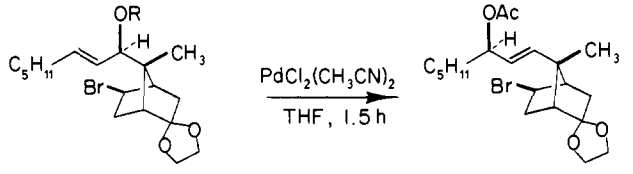
into 12-methyl-$PGF_{2\alpha}$, identical with a sample prepared on a previous occassion[5] by comparison of spectral properties (^1H NMR, IR) and TLC mobility in several solvent systems. It is important to note that the success of the transformation of **6** into **7** was dependent not only on the suprafacial nature of the palladium(II) catalyzed rearrangement but also upon the exclusive preference for *trans*-allylic acetate **7** over *trans*-allylic acetate **8**, since under the reaction conditions the catalyst would be expected to set up an equilibrium between **7** and **8** as well. The exclusive formation of **7** during the conversion of **6** → **7** is undoubtedly due to the conformational rigidity of the bicyclo[2.2.1]heptane ring system coupled with the presence of the bulky C(5) exo-oriented bromine atom and the C(7) methyl group. The highly encumbered C(13) carbon atom (prostaglandin numbering) minimizes steric congestion by preferring sp^2 over sp^3 hybridization, thus driving the equilibrium in favor of **7**.

In a second series of experiments, 1-lithio-1-*trans*-heptene (**9**)[4a] was added to aldehyde **2** affording an 87% isolated yield of allylic alcohol **10**, R_f 0.58 (1:1 hexane–ether).[11] Acetylation of **10**



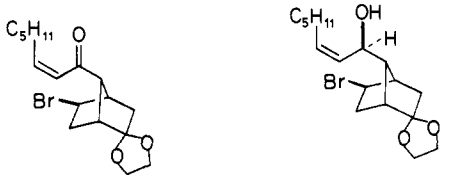
10, R = H

11, R = Ac

12

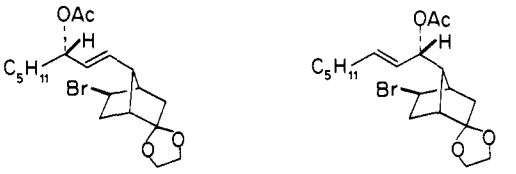
followed by rearrangement provided (93%) as the sole product allylic acetate **12**. The identity of **12** was unambiguously established by transformation into 15-epi-12-methyl-$PGF_{2\alpha}$.[5]

Additional experimentation substantiated the results described above concerning chirality transfer. Allylic alcohol **14**, *prepared*



13 14

in 84% isolated yield by reduction [$LiAlH(OCH_3)_3$,[12] *THF, −100 °C*] *of cis-enone* ***13***,[13] was converted into the corresponding acetate and subjected to the rearrangement conditions [$PdCl_2(CN_3CN)_2$, THF, 2 h]. There was obtained in 90% yield an 85:15 mixture, respectively, of the desired *trans*-allylic acetate **15**[14] and the C(13) *trans*-allylic acetate **16**. The observed ratio of **15**:**16** is not totally unexpected in view of the decreased steric congestion about C(13)

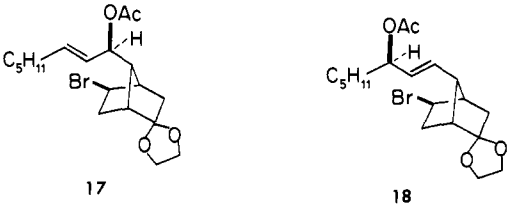


15 16

relative to the example described above (cf. **7** and **8**), where C(13) is pseudoneopentyl in nature.

It was indeed reassuring to find that the same 85:15 ratio of **15**:**16** which was achieved above under equilibrating conditions employing the *cis*-allylic acetate corresponding to **14** could also be realized by using an authentic sample of pure *trans*-allylic acetate **16**.[13]

Similarly the acetate **17**[13] gave way under equilibrating con-



17 18

ditions to a 86:14 mixture, respectively, of the rearranged allylic acetate **18** and starting acetate **17**.

It is clear from the studies above that one can rely upon the palladium(II)-catalyzed [3,3]-sigmatropic rearrangement of allylic acetates for the facile transfer of chirality. In particular, the methodology offers a mild, general solution to the problem of controlling stereochemistry at "C(15)" in rigid bicyclo[2.2.1]-heptane intermediates along the pathway to prostaglandins.

Acknowledgment. Generous support of this work by the National Institute of Child Health and Human Development, National Institutes of Health (Grant HD 14646), and G. D. Searle and Co. is gratefully acknowledged.

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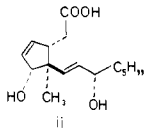
Received August 4, 1980

α-Chloro Boronic Esters from Homologation of Boronic Esters

Sir:

The potential value of α-haloalkaneboronic esters for carbon–carbon bond formation has been apparent since our first report of their behavior toward Grignard reagents,[1] and their utility for joining sterically hindered alkyl groups has been demonstrated elsewhere.[2] However, the various known routes to α-halo boronic esters[2-5] have lacked the generality and convenience needed for widespread synthetic utility.

(9) Compound **7** was smoothly transformed [(a) K_2CO_3, MeOH; (b) DBU, DMF, 160 °C, 16 h; (c) 10% HCl–THF (1:3); (d) H_2O_2, NaOH, MeOH, 0–5 °C, 24 h] into hydroxy carboxylic acid ii which was taken to



ii

12-methyl-$PGF_{2\alpha}$ by conventional means.[10]

(10) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5676. Grieco, P. A.; Yokoyama, Y.; Withers, G. P.; Okuniewicz, F. J.; Wang, C.-L. J. *J. Org. Chem.* **1978**, *43*, 4178.

(11) In addition, approximately 10% of the corresponding isomeric allylic alcohol (R_f 0.39) was isolated.

(12) Brown, H. C.; Hess, H. M. *J. Org. Chem.* **1969**, *34*, 2206.

(13) The straightforward preparation of this substance will be detailed in the full account of this work.

(14) The structure of **15** was unambiguously established by transformation via conventional means into racemic $PGF_{2\alpha}$ methyl ester, mp 66–67 °C (lit.[15] 66.3–67.0 °C).

(15) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745.

(1) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599–603.

(2) Brown, H. C.; De Lue, N. R.; Yamamoto, Y.; Maruyama, K. *J. Org. Chem.* **1977**, *42*, 3252–4. Brown, H. C.; De Lue, N. R.; Yamamoto, Y.; Maruyama, K.; Kasahara, T.; Murahashi, S.; Sonada, A. *Ibid.* **1977**, *42*, 4088–92.

(3) Matteson, D. S.; Liedtke, J. D. *Chem. Ind. (London)* **1963**, 1241. Matteson, D. S.; Schaumberg, G. D. *J. Org. Chem.* **1966**, *31*, 726–31. Matteson, D. S.; Cheng, T. C. *Ibid.* **1968**, *33*, 3055-3060.

(4) Matteson, D. S.; Arne, K. *J. Am. Chem. Soc.* **1978**, *100*, 1325–6.

(5) Rathke, M. W.; Chao, E.; Wu, G. *J. Organomet. Chem.* **1976**, *122*, 145–9.

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Table I. Conversion of Boronic Esters (1) to Homologous α-Chloro Boronic Esters (3)

$RBO_2C_2R'_4$ (1)				$RCHClBO_2C_2R'_4$ (3)		
R	R'	ref or bp[b]	method[a]	yield, %	bp, °C (torr)	NMR, *CH*Cl, δ[c]
$CH_3(CH_2)_3$	H	12a	A	80	75–79 (4)	3.43
$CH_3(CH_2)_3$	CH_3	12b	B	86	50–51 (0.06)	3.50
$(C_2H_5)(CH_3)CH$	H	37–38 (12)	A	77	88–90 (5)	3.52, 3.60[d]
$(CH_3)_3C$	H	28–30 (12)	A	78[e]	61–62 (2)	3.37
c-C_5H_9	H	57–58 (5)	A	82	83–85 (1)	3.50
c-C_6H_{11}	H	12c	A	86	87–89 (0.25)	3.26
CH_2=CH	CH_3	34–37 (7)	A[f]	90	67–70 (2)	4.07
CH_2=$CHCH_2$	CH_3	50–53 (5)	A	87	50–52 (0.3)	3.39
$C_6H_5CH_2$	H	12d	A	84	90–94 (0.15)	3.50
4[a]		60 (0.03)	A[a,g]	86	93–94 (0.06)	3.55
5[a]		95 (0.03)	A[a,g]	67	119–121 (0.03)	3.98
7[a]		67–70 (0.07)	B	84	99–101 (0.05)	3.42, 3.68[d]
9[a]		109–111 (0.07)	B	81[h]	100–140 (0.2)[h]	3.60, 3.66[d]

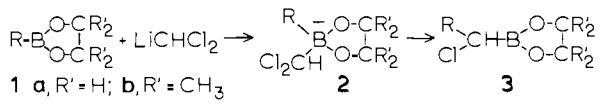
[a] See text. [b] °C (torr), analytical sample. [c] Splittings in accord with assigned structures, line widths 2–4 Hz. [d] Diastereoisomers. [e] Contained a few percent impurity not removed by distillation; hydrolyzed to boronic acid and reesterified for analytical sample. [f] Scale was 0.1 mol. Method B gave only 47%. [g] Heated to completion. [h] Impure because of partial decomposition during distillation. Volatile decomposition products were partially removed from the distilled sample by molecular distillation, 50–65 °C (0.01 torr). Anal. C, H, B; Cl, calcd 10.05, found 9.21.

Table II. Reactions of α-Chloro Boronic Esters (3) with Nucleophiles

$RCHClBO_2C_2R'_4$ (3)			product		
R	R'	nucleophile	structure	bp, °C (torr)	yield, %
c-C_5H_9	H	NaSPh	$C_5H_9CH(SPh)BO_2C_2H_4$	120–124 (0.2)	91
$(CH_3)_3C$	H	NaSPh	$(CH_3)_3CCH(SPh)BO_2C_2H_4$[a]	105–110 (0.15)	88
c-C_5H_9	H	PhMgBr	$C_5H_9CH(Ph)BO_2C_2H_4$	90–93 (0.1)	90
c-C_5H_9	H	*n*-C_4H_9Li	$C_5H_9CH(C_4H_9)BO_2C_2H_4$	85–89 (2.8)	92
c-C_5H_9	H	c-$C_6H_{11}MgCl$	$C_5H_9CH(C_6H_{11})BO_2C_2H_4$	85–88 (0.1)	94
n-C_4H_9	CH_3	$LiOCH_2Ph$	**9**[b]	109–111 (0.07)	93
CH_2=CH (6)	CH_3	*t*-BuO_2CCH_2Li[c]	**7**[b]	67–70 (0.07)	80
CH_2=CH (6)	CH_3	*t*-BuO_2CCH_2Li[d]	**8**[b] (and **7**[e])	82–83 (0.05)	40[e]
10[b]		CH_3MgBr	**12**[b]	85–90 (0.07)	71[b,f]

[a] Anal. H, B, S; C, calcd 62.42, found 63.14. [b] See text. [c] Made with excess *t*-BuOAc. [d] Made with excess LDA. [e] Yield of 7, 22%, total 62%, by NMR analysis of once-distilled product. [f] Overall yield from 9.

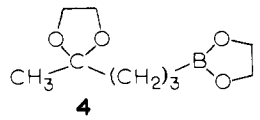
Boronic esters **1** have been homologated with [(trimethylsilyl)chloromethyl]lithium,[6] and there is precedent for the rearrangement of dichloromethaneboronates **2** to α-chloro boronic esters **3** in the reported use of diisopropyl dichloromethaneboronate to homologate RLi to RCHO.[5]



1 a, R' = H; b, R' = CH_3 2 3

We have now found that boronic esters **1** react rapidly with (dichloromethyl)lithium at −100 °C (method A)[7] to form **2**, which rearrange at 20 °C or above to the α-chloro boronic esters **3** in high yields (Table I).[8] The products **3** may be further converted to more complex or functionalized boronic esters **1** (Table II), with the inherent possibility of repeated homologation and structural elaboration. The homologation process tolerates carboxylic ester substituents, though ketones have to be protected. β-Alkoxy boronic esters have been found stable enough toward boron–oxygen β elimination to permit use in synthesis. (Dichloromethyl)lithium generated in situ[9] at −78 °C homologates pinacol boronic esters **1b** (method B).[10]

Unfunctionalized boronic esters **1** as well as the ketal **4** were derived from Grignard reagents.[11,12] Pinacol boronic esters **1b** are stable to water and oxygen. Catecholborane[13] hydroborated methyl 4-pentenoate to **5**.



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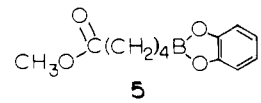

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The other funtionalized boronic esters were obtained from reactions of α-chloro boronic esters **3** with nucleophiles (Table II).[14] Pinacol 3-chloro-1-propene-3-boronate (**6**) gave two products with *tert*-butyl lithioacetate. The simple C-alkylation product **7** was produced exclusively in high yield whenever excess *tert*-butyl acetate was present, regardless of whether the solvent was hexane or THF or contained triglyme and whether the *tert*-butyl lithioacetate was in solution or suspension. The structure

(6) Matteson, D. S.; Majumdar, D. *J. Organomet. Chem.* **1980**, *184*, C41–C43.

(7) (Dichloromethyl)lithium was prepared by Rathke's procedure,[5] modified so that the butyllithium was chilled before mixing, either by running it down the inside of the cold flask or by having the syringe needle tip within 5 mm of the cold liquid. Addition time was 5–10 min for 10–100 mmol. The precipitate of $LiCHCl_2$ dissolved immediately on injection of the boronic ester (~0.9 equiv). The solution was kept at 20 °C overnight, treated with dichloromethane or hexane to precipitate lithium chloride, filtered, and distilled. Rearrangement of intermediates **2** from **4** and **5** required melting the **2** (80–100 °C) under vacuum, and the **2** and **9** were refluxed 10 min in THF to ensure completion.

(8) All new compounds were characterized by ^1H NMR and acceptable analyses (±0.4%) for all elements except oxygen, except as noted.

(9) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325–8.

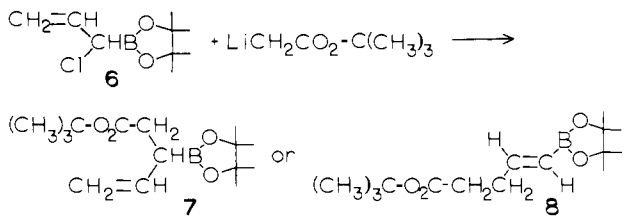
(10) Lithium diisopropylamide (LDA) (12 mmol) in hexane was fluidized with a little THF and added dropwise to **1b** (10 mmol) and dichloromethane (1 mL) in dimethoxyethane (10 mL) at −78 °C. After 1–2 h at 20 °C, the product was distilled.

(11) Boronic acids: Washburn, R. M.; Levens, E.; Albright, C. F.; Billig, F. A. "Organic Syntheses"; Wiley, New York, 1963; Collect. Vol. IV, pp 68–72. Esterification with ethylene glycol or pinacol hydrate to form **1** was conveniently accomplished by stirring the reactants with ether until dissolved, adding hexane to aid separation of water and any excess diol, and distilling.

(12) Known **1**: (a) Laurent, J. P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1962**, *254*, 866–8. (b) Mendoza, A.; Matteson, D. S. *J. Org. Chem.* **1979**, *44*, 1352–4. (c) Tokuda, M.; Chung, V. V.; Inagaki, K.; Itoh, M. *J. Chem. Soc., Chem. Commun.* **1977**, 690–1. (d) Korcek, S.; Watts, G. B.; Ingold, K. U. *J. Chem. Soc., Perkin Trans. 2* **1972**, 242–8.

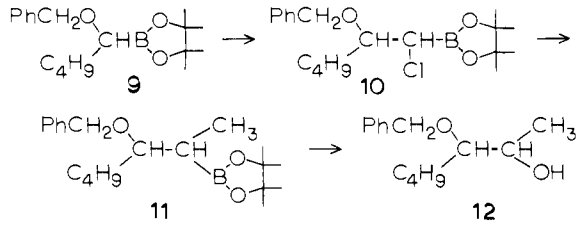
(13) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 1816–8.

(14) The reactants were mixed in THF at −78 °C and the mixture was kept at 20 °C overnight, filtered (Li or Na salts) or given aqueous workup (Mg salts), and distilled. Preparation of **9** was preferably carried out in 1,2-dimethoxyethane, with brief reflux to ensure completion.



of **7** was confirmed by the vinyl pattern in the NMR at δ 5.1 (m, 2, $=CH_2$) and 5.9 (m, 1, =CH). When excess LDA was used in the prepartion of the lithioacetate, up to 65% of the product was **8**, perhaps produced by O-alkylation and Cope rearrangement. The two products were readily separable by distillation, and the structure of **8** was confirmed by the characteristic *trans*-alkeneboronic ester pattern[15] in the NMR at σ 5.55 (d, J = 19 Hz, =CHB) and 6.66 (m, HC=CB). Structures **7** and **8** were further confirmed by resolution with the shift reagent $Eu(fod)_3$.

Homologation of pinacol 1-(benzyloxy)pentane-1-boronate (**9**) (method A) followed by treatment of the crude α-chloro-β-(benzyloxy)alkaneboronic ester **10** with methylmagnesium bromide yielded the β-benzyloxy boronic ester **11**. Both **10** and **11** were unstable to distillation, partially decomposing by boron-oxygen β elimination, but oxidation of crude **11** with alkaline sodium perborate[16] yielded 3-(benzyloxy)-2-heptanol (**12**), 71% based on **9**.



The utility of these reactions in synthesis is limited by the formation of mixtures of diastereoisomers. Chiral control of the homologation process is described in the following communication.[17]

Acknowledgment. We thank the National Science Foundation for support (Grant No. CHE 77-11283).

(15) Matteson, D. S.; Jesthi, P. K. *J. Organomet. Chem.* **1976**, *110*, 25-37.
(16) Matteson, D. S.; Moody, R. J. *J. Org. Chem.* **1980**, *45*, 1091-5.
(17) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.*, following paper in this issue.

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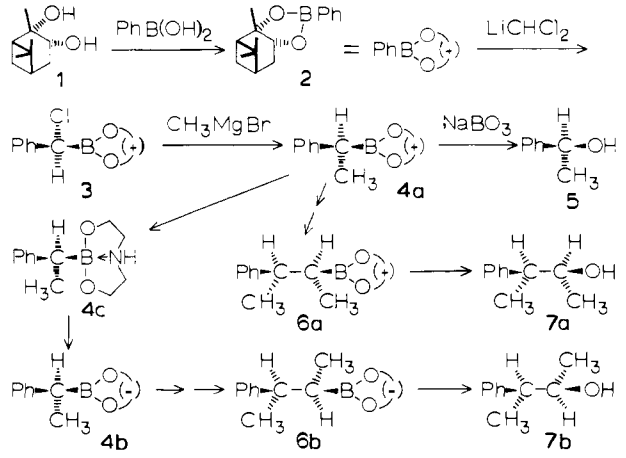
Received August 4, 1980

Directed Chiral Synthesis with Pinanediol Boronic Esters

Sir:

The efficient homologation of boronic esters to α-chloro boronic esters reported in the preceding communication[1] and the availability of (+)-pinanediol[2] (**1**) from (+)-α-pinene,[3] as well as the enantiomer from (-)-α-pinene, by our osmium tetraoxide catalyzed hydroxylation[4] provide the basis for a promising new approach to directed chiral synthesis. To demonstrate, we have synthesized the known[5] (2*S*,3*S*)-3-phenyl-2-butanol (**7a**) (erythro isomer) and (2*R*,3*S*)-3-phenyl-2-butanol (**7b**) (threo isomer) from optically pure (+)-pinanediol benzeneboronate[6] (**2**) by double homologation and subsidiary transformations. Diastereoselectivities achieved were 97% (±1%) in the first homologation and 92-95% in the second homologations leading to **7a** and **7b**.

Scheme I



Semiquantitative exploratory experiments, summarized briefly in the final paragraph, established that homologation of boronic esters of (+)-pinanediol with (dichloromethyl)lithium yields αS α-chloro boronic esters but that prolonged exposure of these products to the chloride ion produced in the reaction may result in significant epimerization. Crystallization of the complex salt of (+)-pinanediol (**1**) with basic sodium borate was observed, which leads to enantiomerically pure **1** on regeneration with cold dilute acid.[7] On the basis of these results, the following efficient syntheses of **7a** and **7b** were designed directly.

(+)-Pinanediol benzeneboronate[6,8] (**2**) was added to (dichloromethyl)lithium[1] at -100 °C and the mixture was kept at 0 °C for 1 h, cooled to -78 °C, treated with methylmagnesium bromide, and kept at 20 °C overnight.[9] The resulting (+)-pinanediol (*S*)-1-phenylethaneboronate (**4a**) (94%) was found to contain 96.8% (±1%) *S* isomer, as estimated by oxidation with alkaline sodium perborate[10] to (*S*)-1-phenylethanol[11] (**5**) (100%), which was converted to the acetate ester for precise measurement of optical rotation,[12,13] enantiomeric excess (ee) 93.7%. The absolute configurations of the boronic esters **3** and **4a** are assigned

(1) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) The rotation is low, $[\alpha]_D$ +3.3°: Schmidt, H. *Chem. Ber.* **1960**, *93*, 2485-90.
(3) Absolute configuration: Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5483-93. Commercial (+)-α-pinene, 92% ee, and (-)-α-pinene, 82% ee, were used.
(4) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449-50.
(5) Cram, D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863-70, 3883-9.
(6) $[\alpha]^{23}_D$ +17.9° (8%, benzene).
(7) Crystallizes as $(C_{10}H_{16}O_2)_2B^-Na^+\cdot 2H_2O$ from THF/water, recrystallized from 95% ethanol/2-propanol. Treatment with 1 equiv of dilute hydrochloric acid, extraction with several portions of petroleum ether, and distillation regenerates **1**, contaminated with varying amounts of its boric acid ester, which does not interfere with synthetic use. Optical purity was determined on the derived benzeneboronate ester **2**.
(8) New compounds were characterized by ^1H NMR and satisfactory analyses (±0.4%) were obtained for all elements except oxygen, except for α-chloro boronic esters (**10**), of which only the homologation product from **4a** has been analyzed satisfactorily to date.
(9) Stoichiometric amounts of reactants were used, with 60 mL of THF solvent for 24 mmol. The product was worked up with aqueous acid, extraction with ether, and Kugelrohr distillation at 130-135 °C (0.1 torr): purity was confirmed by ^1H NMR.
(10) Matteson, D. S.; Moody, R. J. *J. Org. Chem.* **1980**, *45*, 1091-5. Sufficient conditions for these hindered boronic esters, 1 M in 1:1 THF/water, included 5-10% excess sodium perborate, 0.5 equiv of sodium hydroxide, and 15 h at 25 °C. Most samples were refluxed. On addition of petroleum ether, sodium pinanediol borate crystallized, and the other alcohol was purified by extraction and Kugelrohr distillation.
(11) Jacques, J.; Gros, C.; Bourcier, S. "Stereochemistry"; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. 4.
(12) Obsd $[\alpha]^{23}_D$ -116.7° (3%, benzene) (lit.[13] $[\alpha]^{21}_D$ -124.5°).
(13) Huisgen, R.; Rüchardt, C. *Justus Liebigs Ann. Chem.* **1966**, *601*, 21-34.

0002-7863/80/1502-7590$01.00/0