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Communications

Consecutive Hydroacylation and Reduction of 1-Alkyne with 2-(Diphenylphosphino)benzaldehyde by Rh(I)

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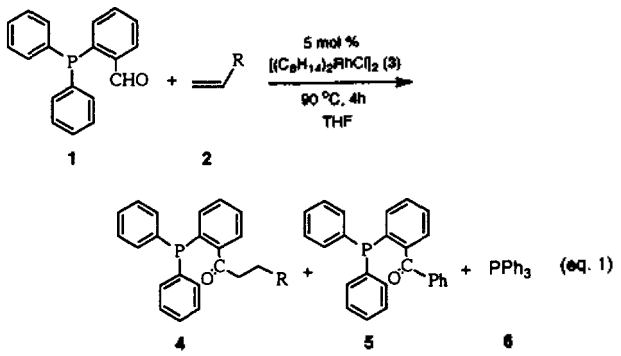
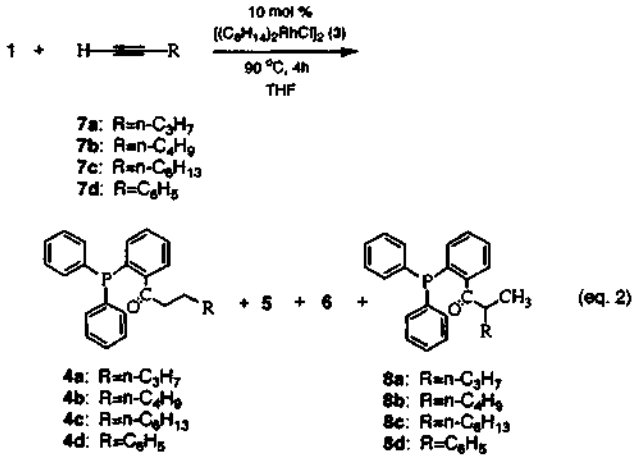
One of good ways to make C-C bond in organic synthesis is hydroacylation which is addition reaction of an aldehyde C-H bond across an alkene under transition metal catalyst.[1] Although intramolecular hydroacylation has been studied in detail,[2] limited number of intermolecular hydroacylations have been documented[1] in spite of its usefulness. The major problem for intermolecular hydroacylation is the competition with decarbonylation, which has been used for elimination of aldehyde functional group in organic compounds.[3] In order to solve its limitation, some model compounds such as 8-quinolinecarboxaldehyde,[4] aldimine,[5] 2-(diphenylphosphino)benzaldehyde[6] were applied for hydroacylation. Already hydroacylation of 1-alkene with 2-(diphenylphosphino)benzaldehyde has been studied (eq. 1).[7] Reaction of 2-(diphenylphosphino)benzaldehyde (**1**) and 1-alkene (**2**) in THF at 90℃ for 4 h in the presence of $[(C_8H_{14})_2RhCl]_2$ (**3**) as a catalyst (5 mol%) gave a mixture of **4**, **5** and **6**.[7] While **4** was the major hydroacylated product, compound **5** and **6** supposed to be the ones derived from P-C bond cleavage and decarbonylation of **1**. Since hydroacylation of 1-alkyne with aldehyde supposed to give α,β-unsaturated ketone,[8] 1-alkyne is another interesting substrate. This report deals with consecutive hydroacylation and reduction of 1-alkynes with 2-(diphenylphosphino)benzaldehyde as a model compound under Rh(I) catalyst.



1 2 4 5 6 (eq. 1)

When **1** was reacted with 1-pentyne (**7a**) in THF at 90℃ for 4 h in the presence of **3** as a catalyst (10 mol% based upon **1**), a mixture of **4a**, **5** and **6** was obtained in a 74 : 3 : 23 ratio, determined by gas chromatography (eq. 2).[9] Hydroacylated product, **4a** was isolated in 30% yield (based on **1**)

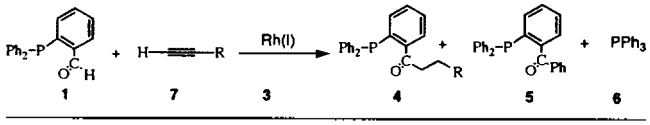


1 + H—≡—R → + 5 + 6 + (eq. 2)

along with a small amount of branched alkyl ketone **8a**, determined by GC-MSD.[10] Saturated alkyl ketone **4a** and **8a** were unexpected products for this reaction,since hydroacylation of 1-alkyne should have given α,β-unsaturated ketone.[8] Any initial hydroacylated product, α,β-unsaturated ketone, was not determined. Other 1-alkynes could also be used for this hydroacylation under identical reaction condition. The results are summarized in Table 1.

When **1** was reacted with 1-hexyne (**7b**), 1-octyne (**7c**) and phenyl acetylene (**7d**) in different mole ratios of substrates, corresponding saturated alkyl ketones, **4b**, **4c**[11] and **4d** were obtained with a trace amount of branched alkyl ketone **8**.[10] The first step for this hydroacylation must be aldehyde C-

Table 1. Hydroacylation of 1-Alkyne (7) with 2-(Diphenylphosphino)benzaldehyde (1)

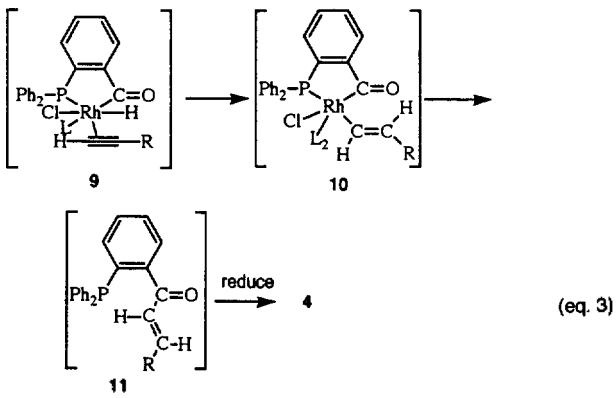


1 7 3 4 5 6

Entry	R	mole ratio of 1 : 7	Ratio[a] of 4/5/6	Isolated Yield of 4
1	n-C_3H_5 (7a)	1 : 5	74 : 3 : 23	30%[b]
2	n-C_4H_9 (7b)	1 : 5	98 : 2 : 0	26%[c]
3	n-C_6H_{13} (7c)	1 : 5	90 : 10 : 0	26%
4	C_6H_5 (7d)	1 : 5	98 : 0 : 2	23%[d]
5	n-C_3H_5 (7a)	3 : 1	79 : 12 : 9	75%
6	n-C_4H_9 (7b)	3 : 1	73 : 23 : 4	84%[e]
7	n-C_6H_{13} (7c)	3 : 1	76 : 19 : 5	88%[f]
8	C_6H_5 (7d)	3 : 1	61 : 39 : 0	53%

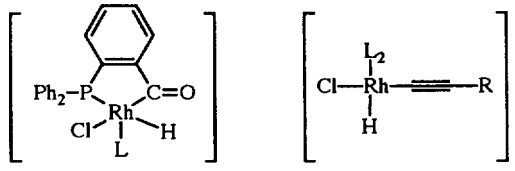
[a]All reactions were carried out in THF at 90℃ for 4h under 10 mol% of $[(C_8H_{14})_2RhCl]_2$ (3). Product yield lower than 1% is ignored.; [a]Product ratio was determined by GC-MSD; [b]contains 2% of branched alkyl ketone (8a); [c]contains 1% of branched alkyl ketone (8b); [d]contains 1% of branched alkyl ketone (8d); [e]contains 2% of branched alkyl ketone (8b); [f]contains 1% of branched alkyl ketone (8c).

H bond cleavage of **1** by Rh(I)[4] and coordination of 1-alkyne to lead intermediate **9** (eq. 3). Hydrometallation of 1-alkyne in **9** might generate acylrhodium(III) *trans*-1-alkenyl complex



(eq. 3)

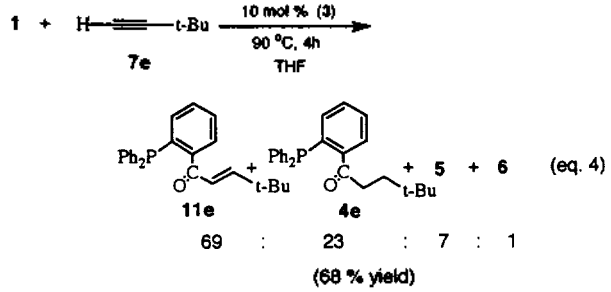
10, and subsequent reductive elimination of **10** affords *trans*-α,β-unsaturated ketone **11**. The reaction could not stop at this stage, and hydride reduction of **11** might produce **4** as a final product. There are two possible hydride sources, acylrhodium(III) hydride **12** and alkynylrhodium(III) hydride **13**, generated from C-H bond cleavage of aldehyde **1** and 1-alkyne **7** by Rh(I).



12 13

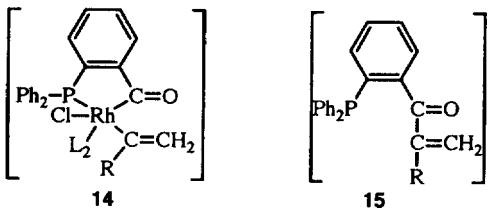
If **12** reduces **11** to **4**, at least 3 equivalents of **1** based upon **7** should be needed. That is, one equivalent of **1** must be used for hydroacylation of 1-alkyne to give α,β-unsaturated ketones and two equivalents of **1** for the subsequent reduction of α,β-unsaturated ketone. When the reactions were carried out in a 1 : 5 mole ratio for **1** and **7**, 23-30% yields of hydroacylated products were isolated based upon **1** (Table 1. entries 1-4). By contrast, when the reactions were carried out in a 3 : 1 mole ratio for **1** and **7**, in which a limiting reactant was **7**, 53-88% yield of hydroacylated products based upon **7** were isolated (Table 1. entries 5-8). These results explain that the hydride source for reduction must be **12** generated from C-H bond cleavage of **1** with Rh(I). Reactivity of intermediate **11** might be much higher than that of **7** towards acylrhodium(III) hydride, since **11** could not be isolated.

When 3,3-dimethyl-1-butyne (**7e**), a sterically hindered 1-alkyne, was applied for this hydroacylation (1 : 5 mole ratio of **1** and **7e**) in order to identify the generation of the intermediate **11**, *trans*-α,β-unsaturated ketone **11e**, **4e**, **5** and **6** were obtained in a 69 : 23 : 7 : 1 ratio in 68% yield.[12] (eq. 4) The reason for isolation of large amount of **11e** must



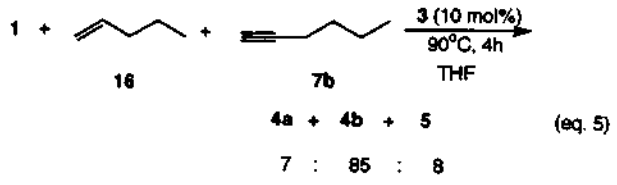
(eq. 4)

be that sterically hindered t-butyl group retards the metal-hydride approach to the olefin in **11e** to reduce it. Exclusive *trans*-olefin formation (**11e**: $J_{CH=CH}$ = 16.0 Hz) ensures the mechanism involving the intermediates **10** and **11** in eq. 3. From the above result, it is clear that branched alkyl ketone **8** might be also produced from the reduction of **15** *via* initial hydrometallation intermediate **14**.



14 15

When **1** was reacted with an equimolar mixture of 1-pentene (**16**) and 1-hexyne (**7b**) under the identical previous reaction condition to compare the reactivity of 1-alkene with that of 1-alkyne for hydroacylation, a mixture of **4a**, **4b** and **5** was isolated in a 7 : 85 : 8 ratio in 31% yield (eq. 4).



(eq. 5)

This result indicates that 1-alkyne has much higher reactivity (about 12 times) than 1-alkene. The strong coordination power of 1-alkyne compared with that of 1-alkene to the transition metals might be a major role for the greater reactivity of 1-alkyne than that of 1-alkene.[13]

In conclusion, hydroacylation of 1-alkyne with 2-(diphenylphosphino)benzaldehyde (**1**) with Rh(I) catalyst (**3**) afforded a mixture of 2-(diphenylphosphino)alkanophenone **4**, **5**, and **6**, identical products prepared from hydroacylation of 1-alkene with a trace amount of branched alkyl ketone **8**. The reason for the formation of saturated alkyl ketone must be that hydroacylation of 1-alkyne with aldehyde generates *trans*-α,β-unsaturated ketone and subsequent hydride reduction generated from C-H bond cleavage by Rh(I) leads to saturated alkyl ketone. Clear reduction mechanism of α,β-unsaturated ketone by rhodium(III)hydride generated from C-H bond cleavage of **1** is under study.

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9. Treatment of reagents carried out under argon in dry box. Some corresponding phosphine oxides were obtained during silica-gel column chromatography separation after the reaction.
10. Since hydroacylated branched alkyl ketone **8a** was hardly isolated due to presence of a small amount (2%), detection was only possible by GC-MSD. Characteristic mass peak of $Ph_2PC_6H_4C(OH)=CH(CH_3)^+$, 318, McLafferty rearranged fragment derived from the branched alkyl ketones such as **8a**, **8b**, **8c** and **8d** has been shown. **8a**: mass spectrum (assignment, relative intensity) 360 (M^+, 3.9), 345 (M^+-CH_3, 16.2), 318 ($Ph_2PC_6H_4C(OH)=CH(CH_3)^+$, 23.7), 317 ($M^+$-$C_3H_7$, 100), 303 ($Ph_2PC_6H_4C(OH)=CH^+$, 3.3), 221 (6.5), 183 (15.5); **8b**: mass spectrum (assignment, relative intensity) 374 (M^+, 6.1), 359 (M^+-CH_3, 10.9), 318 ($Ph_2PC_6H_4C(OH)=CH(CH_3)^+$, 28.1), 317 ($M^+$-$C_4H_9$, 100), 303 ($Ph_2PC_6H_4C(OH)=CH^+$, 6.6), 221 (6.7), 183 (11.8); **8c**: mass spectrum (assignment, relative intensity) 403 (MH^+, 4.4), 402 (M^+, 4.1), 388 (MH^+-CH_3, 16.4), 387 (M^+-CH_3, 13.1), 318 ($Ph_2PC_6H_4C(OH)=CH(CH_3)^+$, 27.9), 317 ($M^+$-$C_6H_{13}$, 100), 303 ($Ph_2PC_6H_4C(OH)=CH^+$, 5.9), 201 (7.3), 183 (12.5); **8d**: mass spectrum (assignment, relative intensity) 395 (MH^+, 22.8), 394 (M^+, 25.2), 380 (MH^+-CH_3, 100), 379 (M^+-CH_3, 89.3), 318 ($Ph_2PC_6H_4C(OH)=CH(CH_3)^+$, 19.9), 303 ($Ph_2PC_6H_4C(OH)=CH^+$, 13.0), 207 (26.1), 183 (38.7). **8e**: mass spectrum (assignment, relative intensity) 374 (M^+, 17.7), 359 (M^+-CH_3, 66.3), 318 ($Ph_2PC_6H_4C(OH)=CH(CH_3)^+$, 16.7), 317 ($M^+$-$C_4H_9$, 100), 303 ($Ph_2PC_6H_4C(OH)=CH^+$, 46.2), 201 (32.5), 183 (31.6).
11. Spectroscopic analysis of **4c**. **4c**: ^{1}H NMR (100 MHz, $CDCl_3$) δ (ppm) 7.85-7.27 (m, 14H, $2C_6H_5$ & C_6H_4), 2.72 (t, J=7.1 Hz, 2H, α-CH_2 to CO), 1.25-0.85 (m, 15H, n-C_7H_{15}); IR spectrum (neat) 3059, 2921, 2855, 1677 (CO), 1585, 1440, 1295, 1203, 1124, 999, 933, 755, 597 cm^{-1}; mass spectrum (assignment, relative intensity) 403 (MH^+, 6.3), 373 (M^+-C_2H_5, 2.3), 359 (M^+-C_3H_7, 4.3), 317 (M^+-C_6H_{13}, 3.0), 304 ($Ph_2PC_6H_4C(OH)=CH_2^+$, 26.5), 303 (M^+-C_5H_{11}, 100), 225 (12.9), 183 (9.3).
12. The ratio was determined by GC and a trace amount (<0.5%) of branched alkyl ketone **8e** was obtained. **11e** was partially oxidized to give phosphine oxide form of **11e** during chromatographic separation. Spectroscopic analysis of **4e** and **11e**. **4e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.89-7.03 (m, 14H, $2C_6H_5$ & C_6H_4), 2.90 (t, J=8.0 Hz, 2H, α-CH_2 to CO), 1.55 (t, J=8.6 Hz, 2H, β-CH_2 to CO), 0.89 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 209.97 (CO), 138.22-128.15 (Cs of three phenyl group), 37.83 (β-C to CO), 35.84 (α-C to CO), 31.26 (γ-C to CO), 29.13 (3Cs of $3CH_3$); IR spectrum (neat) 3059, 2967, 2875, 1703 (CO), 1591, 1440, 1367, 1262, 1203, 1124, 933, 749, 696 cm^{-1}; mass spectrum (assignment, relative intensity) 375 (MH^+, 2.2), 374 (M^+, 8.7), 359 (M^+-CH_3, 6.3), 317 (M^+-C_4H_9, 3.7), 304 ($Ph_2PC_6H_4C(OH)=CH_2^+$, 21.3), 303 (M^+-C_5H_{11}, 100), 225 (13.9), 183 (18.2). **11e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70-7.27 (m, 14H, $2C_6H_5$ & C_6H_4), 6.85 (d, J=16.0 Hz, 1H, β-CH to CO), 6.61 (d, J=16.0 Hz, 1H, α-CH to CO), 1.03 (s, 9H, CH_3); mass

spectrum (assignment, relative intensity) 373 (MH^+, 7.4), 372 (M^+, 28.3), 358 (MH^+-CH_3, 32.4), 357 (M^+-CH_3, 100), 343 (MH^+-$2CH_3$, 12.9), 315 (M^+-$(CH_3)_3C$, 38.2), 303 (16.3), 295 (M^+-Ph, 5.5), 221 (15.0), 201 (26.5), 183 (52.3). Oxide form of **11e**: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70-7.27 (m, 14H, $2C_6H_5$ & C_6H_4), 6.46 (d, J=16.0 Hz, 1H, β-CH to CO), 6.17 (d, J=16.0 Hz, 1H, α-CH to CO), 1.04 (s, 9H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 195.44 (CO), 134.87-123.36 (Cs of three phenyl group), 33.99 (γ-C to CO), 28.39 (3Cs of $3CH_3$); IR spectrum (neat) 3059, 2967, 2875, 1966, 1664 (CO), 1571, 1440, 1368, 1302, 1124, 1032, 861, 755, 703 cm^{-1}; mass spectrum (assignment, relative intensity) 389 (MH^+, 8.1), 388 (M^+, 17.8), 373 (M^+-CH_3, 17.4), 332 (MH^+-$C(CH_3)_3$, 16.9), 331 (M^+-$C(CH_3)_3$, 53.5), 319 (11.8), 311 (M^+-C_6H_5, 21.4), 305 ($Ph_2P(=O)C_6H_4CO^+$, 50.4), 303 (27.7), 295 (14.2), 289 (19.0), 277 ($Ph_2P(=O)C_6H_4^+$, 36.0) 227 (28.,2), 201 (20.0), 183 (32.8), 152 (50.0), 77 (100); HRMS calcd for $C_{25}H_{25}O_2P$ (M^+): 388.1594. Found: 388.1569.

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An Efficient and Enantioselective Synthesis of A Chiral Primary Amine II[1]

Kwang Yul Moon, Nakyen Choy, Chihyo Park, Young Chan Son, Won Hee Jung, Ho-il Choi, Chang Sun Lee, Chung Ryeol Kim, Sung Chun Kim*, and Heungsik Yoon*

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Chiral amines have received considerable attention because of their potential as a key intermediate for synthetic drugs such as **1**, which was developed in our lab as a potent and irreversible HIV-1 protease inhibitor.[2]

In our continuing effort to optimize C-terminal of this novel series of inactivators, it was necessary to develop an efficient method for the preparation of optically active primary amines such as **5**. We, herein, report an efficient and enantioselective synthesis of a chiral primary amine using a naturally occurring amino acid as the starting material.

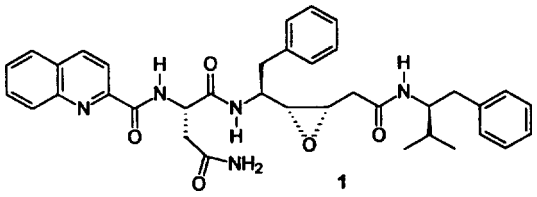
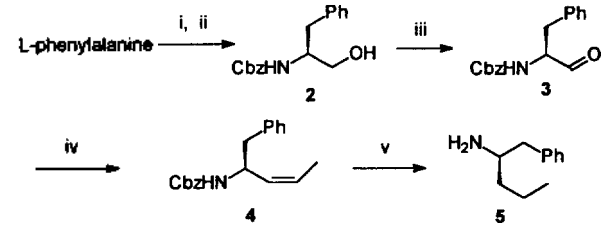
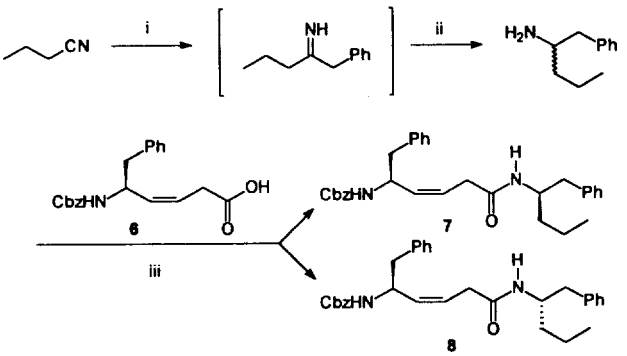


Figure 1. Structure of Irreversible HIV-1 Protease Inactivator.



Scheme 1. Reagents: i) $NaBH_4$, H_2SO_4, 96%; ii) CbzCl, Na_2CO_3, 95%; iii) $(COCl)_2$, DMSO, $^iPr_2NEt$, 98%; iv) ethyltriphenylphosphonium bromide, KHMDS, toluene, −20 ℃, 92%; v) Pd/C, H_2, MeOH, 99%.



Scheme 2. Reagents: i) $PhCH_2MgCl$, THF, reflux; ii) $NaBH_4$, THF/MeOH; iii) isobutyl chloroformate, N-methylmorpholine, CH_2Cl_2, −20 ℃.

As shown in Scheme 1, the target amine **5** was synthesized from L-phenylalanine. Cbz-protected phenylalaninol **2** was readily obtained from L-phenylalanine by $NaBH_4$-H_2SO_4 reduction[3] and subsequent Cbz-protection. Oxidation of **2** was performed under the modified condition[4] of Moffat-Swern oxidation at −20 ℃. Olefination of **3** was effected by use of potassium bis(trimethylsilyl)amide in toluene at −20 ℃ to give **4** without racemization. As a final step, hydrogenation with 10% Pd/C catalyst afforded the target compound **5**. The yields of all the steps in Scheme 1 were higher than 90% (81% overall yield).

The racemic amine was prepared from butyronitrile by the addition of benzylmagnesium chloride and the subsequent $NaBH_4$ reduction of the ketemine intermediate.[1] The coupling of the resulting racemic amine with **6** gave two diastereomers **7** and **8** which can be easily separated[5] on silica gel column chromatography as depicted in Scheme 2.

The coupling of amine **5** from Scheme 1 with **6** gave exclusively one diastereomer **7**, which proved that the reaction sequence shown in Scheme 1 was an efficient and enantioselective method for the preparation of optically active amine **5**.[6]

Various alkyltriphenylphosphonium salts were subjected to the same method in Scheme 1 to provide optically active amines as follows:

Studies are in progress for the extension of this method to prepare various optically active amines by the combination of L- or D-amino acids and alkyltriphenylphosphonium salts.