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Practical Large-Scale Preparation of (±)-2-*exo*-Norbornyl Carboxylic Acid and Its Improved Isolation As the Sodium Salt

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ABSTRACT: A practical, robust, and high-yielding three-step−one-pot procedure for the diastereoselective synthesis of (±)-2-*exo*-norbornyl carboxylic acid starting from norbornylene has been found and demonstrated on multikilogram scale, setting a new benchmark for low-pressure hydroformylation of cyclic, bridged olefins. The newly found, nonhygroscopic crystalline sodium salt of this acid provides a practical isolation point.

INTRODUCTION

Despite its abundant use as building block for a variety of pharmacologically active molecules (for examples, see refs 1−3), the available protocols for the synthesis of racemic *exo*-norbornyl-2-carboxylic acid are still surprisingly unpractical; the traditional iodolactonization method via the commercially available *endo*/*exo* mixture of norborn-2-ene-5-carboxylic acid according to Berson and Ben-Efraim[4] is cumbersome due to the repeated bulb-to-bulb distillations necessary to purify the crude unsaturated *exo*-acid. Furthermore, throughput is poor as a consequence of the low content of *exo*-isomer (*endo*/*exo* 80:20) in the commercial starting material. *exo*-Selective nickel-mediated carboxylation of norbornylene has been reported but has not proven practical due to either the generation of stoichiometric nickel waste [5] or the requirement for specialized electrochemical equipment and selectivity issues.[6] The carbonylation of *exo*/*endo*-norbornan-2-ol in liquid sulfur dioxide−antimony(V) chloride at −70 °C has also been reported to lead selectively to 2-*exo*-norbornane-2-carboxylic acid,[7] but, presumably due to the noxious solvent system and expensive starting material, has not found widespread use. Another direct carboxylation variant that leads to an amide of norbornane-2-carboxylic acid has been reported but appears less straightforward.[17]

On the other hand, hydroformylation of cheap norbornylene has been claimed to give a 95:5-mixture of *exo*- and *endo*-norbornane-2-carbaldehyde in 72% yield by Brunet and Neibecker in 1989 (after fractional vacuum distillation), albeit via a less desireable reagent system (in situ generation of air-sensitive, stoichiometric $KHFe(CO)_4$ from highly toxic iron pentacarbonyl). The authors also claim the selective oxidation of *exo*-norbornane-2-carbaldehyde (**1**) to the corresponding *exo*-acid (**2**) with $KMnO_4$ in 94% yield, although experimental details and configurational (*exo*/*endo*) purity were not given.[8]

Rhodium-catalyzed hydroformylation as a potentially more convenient method for the synthesis of the intermediate aldehyde **1** has been claimed by a German patent from 1973. The reaction was reported to proceed in acceptable yields only at higher temperatures (∼100 °C) and pressures (>1000 psi CO-pressure), and norbornylene was not investigated as substrate.[9]

Since then, curiously few literature reports on transition metal-catalyzed hydroformylations of α-branched olefins have appeared.[10] Especially bridged olefinic systems such as norbornylene have not been studied very well; the reactivity of cyclic olefins is lower, and the reactions are less selective when compared to terminal olefins.[10] A closer look at published reports on this deceptively simple transformation reveals that progress towards a practical low-pressure method for bridged olefins has been painfully slow.[11] In 2005, Huang et al. at Amgen reported an attractive low-pressure (60 psi) rhodium-catalyzed asymmetric hydroformylation of norbornylene using the TangPhos ligand (0.5 mol % Rh-cat. precursor, 0.6 mol % TangPhos).[12] The same report also mentions the oxidation of enantiomerically enriched aldehyde **1** to the carboxylic acid **2** (using $NaClO_2$/cat. TEMPO as oxidant) en route to the corresponding carboxamide, albeit experimental details and characterization data/*exo*/*endo* purity for **2** were not given. Unfortunately, the paper fails to mention that only one enantiomer (*S*,*S*′,*R*,*R*′) of the TangPhos ligand has been commercialized, and the racemate is not sold.[13] Hence, the method is only useful for the synthesis of one enantiomer of the aldehyde **1** and the carboxylic acid **2**.[14]

RESULTS AND DISCUSSION

For one of our development projects, we needed a practical and economic access to large quantities of the racemic *exo*-acid **2**. We set out to reinvestigate the catalytic hydroformylation of norbornene, with the goal of finding low pressure (≤50 psi)

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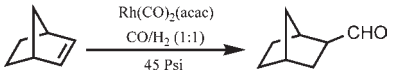
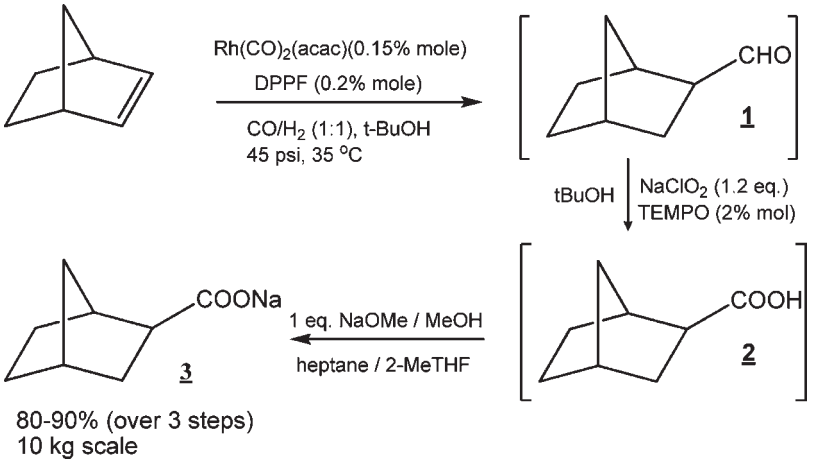
Table 1.[a]



entry	ligand	result
1	$^{t}Bu_3P \cdot BF_4$	multiple CHO-containing products, starting material remaining
2	Ph_3P	product contaminated with a minor (~1−2%) aldehyde byproduct
3	(±)BINAP	slow reaction
4	DPPF	clean product formation
5	XantPhos	clean product formation
6	biphenyl 2-(di^{t}Bu)phosphine	no reaction
7	2′-(*N*,*N*-dimethylamino)biphenyl-2-(dicyclohexyl)Phosphine	multiple CHO-containing products
8	2-biphenyl-dicyclohexylphosphine	multiple CHO-containing products, starting material remaining
9	(oxydi-2,1-phenylene)bis(diphenylphosphine)	clean product formation
10	2′,6′-dimethoxybiphenyl-2-dicyclohexylphosphine	multiple CHO-containing products, starting material remaining
11	2′-(*N*,*N*-dimethylamino)biphenyl-2-diphenylphosphine	multiple CHO-containing products, starting material remaining
12	tri-*O*-tolylphosphine	no reaction
13	tri-2-furylphosphine	product contaminated with two minor (~10%) aldehyde byproducts
14	diphenyl-2-pyridinephosphine	product contaminated with two minor (~10%) aldehyde byproducts

[a] Conditions: toluene, 35 °C, 0.5 mol % Rh-cat., 0.6 mol % ligand, NMR analysis after 22 h.

Scheme 1



conditions with a cheap and readily available ligand, hence allowing scale-up in common multipurpose equipment.

An initial ligand screen (Table 1) quickly identified DPPF as a viable ligand for scale-up. A subsequent solvent screen with this ligand (data not shown) revealed that toluene, isopropyl acetate, acetonitrile, dichloromethane, and *tert*-butanol all give good conversion, with toluene and *tert*-butanol showing the cleanest reaction profiles.

Since we were interested in a procedure that would avoid isolation of the intermediate and somewhat unstable aldehyde, the catalyst loading screen was conducted in *tert*-butanol in order to enable a homogeneous subsequent oxidation step. [A solvent screen of the $NaClO_2$/TEMPO oxidation of **1** to **2** had earlier identified t-BuOH as best solvent both in terms of yield and product quality (*data not shown*).] Combinations of Rh catalyst precursor and DPPF ranging from 0.5/0.6% down to 0.15/0.2% all gave complete conversion by NMR, while a 0.1/0.15% combination still showed ~5% starting material after 20 h. Initial scale-up experiments on multigram scale using a 0.15%/0.2% catalyst/ligand load were conducted at five different temperatures (r.t. (27 °C), 35 °C, 40 °C, 45 and 50 °C). At room temperature, the reaction was incomplete after 20 h, whereas at 50 °C, the reaction was not as clean as in the 35−45 °C range. At 35 °C, a multigram scale-up experiment cleanly proceeded to completion in only two volumes of t-BuOH. Direct, TEMPO-catalyzed bleach oxidation of the intermediate aldehyde **1** [Contrary to the Neibecker procedure (using potassium tetracarbonylhydridoferrate as reagent[8]), which reports a 95:5 *exo*/*endo*-mixture, we observed exclusively the *exo*-isomer (**1**) of the aldehyde at this point.] in the *same solvent* affords the desired acid (±)-**2** which is conveniently isolated in the form of its crystalline and nonhygroscopic sodium salt **3** in excellent yield and configurational (*exo*) purity[15] (Scheme 1). In terms of safety, TSU testing showed both steps to be

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Table 2.

compound	retention time (min)
2 (acid)	6.63
1 (aldehyde)	4.80

benign (data not shown). To the best of our knowledge, this is the first application of a clean and practical hydroformylation in *tert*-butanol and is somewhat surprising given the earlier report of t-BuOH solvent participation by Andrianary and Jenner.[16] A readily available, economic ligand (dppf) is used at very low loading (0.2 mol % at 0.15 mol % Rh-catalyst precursor load), thus setting a new benchmark for the practical low-pressure hydroformylation of bridged olefins (compare ref 11).

The hitherto unknown, well-behaved, and nonvolatile sodium salt **3** is the method of choice to isolate the acid **2** and, for all practical purposes (e.g., formation of derivatives, functional group conversions), can be used instead of the parent acid **2**, which is volatile and much more difficult to crystallize.[18] To the best of our knowledge, this represents the most direct and practical procedure for making and isolating racemic *exo*-norbornane-2-carboxylic acid on-scale and should be applicable to other substituted bicyclic olefins as well.

PROCEDURES

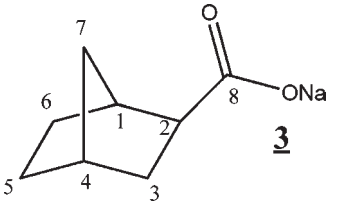
The reaction was scaled up in a 1-L stainless steel Biotage Atlantis reactor. Norbornylene (150 g), t-BuOH (300 mL), $Rh(CO)_2(acac)$ (0.62 g) and DPPF (1.77 g) were charged under nitrogen. Under mechanical stirring, the reactor was purged with nitrogen, then with syngas (H_2−CO 1:1) (total volume ∼0.5 L at this point). The reactor was purged with nitrogen, then purged with syngas, and finally pressurized with syngas to 45 psi; stirring speed was set to 800 rpm, and the internal temperature was set to 35 °C. The reaction was complete (>99% conversion) in about 20 h (NMR-assay). Assay yield and purity >98% (by GC). After cooling to 20−25 °C, this solution of crude aldehyde **1** was transferred to a 3 L-reactor. TEMPO (5 g) was charged, and the mixture was cooled to 10 °C. In a separate 2 L-vessel, $NaH_2PO_4 \times H_2O$ (242 g) was dissolved in water (1 L), to this solution was added $NaClO_2$ (174 g), and the mixture was stirred until a clear solution formed which was precooled to 5−10 °C. Under cooling, this oxidant solution was charged slowly to the vigorously stirred crude aldehyde solution in the 3-L reactor, such that the internal temperature stayed below 25 °C (*caution: exothermic!*). After 30 min, GC showed <0.1% aldehyde and 98% assay yield of acid **2**. Heptane (500 mL) was charged to the reactor. The mixture was stirred for 5 min, and the layers were separated. To the cooled (0 °C) organic layer was slowly added a solution of $Na_2S_2O_3$ (100 g) in water (400 mL) (*Caution: exothermic!*), such that the temperature stayed below 25 °C. The mixture was stirred for 10 min. The aq phase was discarded and the organic phase (checked with KI-starch paper for residual oxidant: negative) stirred with water (300 mL) for 5 min. The aq phase was discarded, and the organic phase was then concentrated and to a residual volume of ∼500 mL. Heptane (500 mL) was charged to the reactor, and the distillation was continued to a final volume of about 0.5 L (60−65 °C reactor temp, 80 °C jacket temp, 45 min distillation time, 910 mL total distillate volume). The solution was cooled to 20−25 °C and stirred at this temperature for 30 min, before filtration through a pad of Celite 545 (10 g)/activated charcoal (10 g)/Celite 545 (10 g). The pad was rinsed with heptane (150 mL). The combined filtrate (0.62 L, GC-assay yield of norbornyl acid **2**: 210 g (94%)) was diluted with 2-methyl-THF (1.8 L), heated to 45−50 °C, and treated with 1 equiv of NaOMe (as determined by assay yield from step 2) (0.325 kg as 25 wt % soln in MeOH, 45 min addition time). After cooling to 20−25 °C over 1.5 h, the resulting slurry was aged for another 1.5 h. The suspension was filtered (polypropylene filter cloth) and the filter cake washed with cold 2-methyl-THF (2 × 250 mL), then dried under nitrogen stream to constant weight. Yield was 0.225 kg (87%). Special hazards associated with the procedure: operate in hood with CO-monitor (*normal safety precautions for CO-reactions apply*) Source of starting materials: all from Aldrich except syngas (Airgas).

Kilolab Scale-Up. Using the protocol outlined above, from 8.0 kg of norbornylene were obtained 11 kg of **3** (80%). Residual solvents: heptane 0.2%, 2-MeTHF: 0.4%, MeOH: 0.04% (all by GC); no other impurities by GC + NMR; water (by KF-Titr.): 0.12%. XRD analysis shows the sodium salt to be crystalline. Mp 218−219 °C decomp. Residual Rh content was below detection limit (<0.01 ppm).

GC Analytical Method. Column: Agilent 1909/J-413, HP-5, 5% phenyl methyl siloxane, capillary 30.0 m × 320 μm × 0.25 μm nominal. Temperature program: 15 °C/min from 60 to 250 °C (see Table 2 for retention times).

NMR: the ^1H and ^{13}C resonances were assigned from the DQCOSY, NOESY, HSQC, and HMBC spectra were acquired on a Bruker DRX-400 spectrometer. Solvent: DMSO/D_2O. The assignments are shown in Table 3. The *exo*-stereochemistry of the carboxyl group is confirmed by the COSY and NOESY spectra. The endoisomer could not be detected. In the COSY spectrum H-2 shows a W′-coupling to the H-7 proton at 1.36 ppm. This, W′-coupling is only possible if H-2 is in the *endo* position. In the NOESY spectrum H-2 shows an NOE to the H6 proton at 1.11 ppm, further confirming the *endo* orientation of H-2.

Table 3. ^1H and ^{13}C assignments of 3 in DMSO-d_6 + D_2O



position	group	^{13}C (ppm)[a]	^1H (ppm)[b]
1	CH	41.13	2.34
2	CH	49.94	1.92
3	CH_2	35.36	1.73, 1.23
4	CH	36.10	2.11
5	CH_2	29.33	1.38, 1.06
6	CH_2	29.84	1.39, 1.11
7	CH_2	36.65	1.36, 0.94
8	C	180.89	–

[a] Relative to DMSO-d_6 referenced as 39.50 ppm. [b] Relative to TMS referenced as 0.00 ppm.

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REFERENCES

(1) Henriksson, M.; Homan, E.; Johansson, L.; Vallgarda, J.; Williams, M.; Bercot, E. A.; Fotsch, C. H.; Li, A.; Cai, G.; Hungate, R. W.; Yuan, C. C.; Tegley, C.; St. Jean, D. J., Jr.; Han, N.; Huang, Q.; Liu, Q.; Bartberger, M. D.; Moniz, G. A.; Frizzle, M. J.; Marshall, T. L. WO/2007/061661 A2, May 31, 2007.

(2) Gobbi, L.; Jaeschke, G.; Luebbers, T.; Roche, O.; Rodriguez Sarmiento, R. M.; Steward, L. WO/2007/093540 A1 Aug 23, 2007.

(3) Bennani, Y. L.; Chamberlin, S. A.; Chemburkar, S. R.; Chen, J.; Dart, M. J.; Gupta, A. K.; Wang, L. U.S. Pat. Appl. 2004209858 A1 Oct 21, 2004.

(4) Berson, J. A.; Ben-Efraim, D. A. *J. Am. Chem. Soc.* **1959**, *81*, 4083.

(5) Hoberg, H.; Schaefer, D. *J. Organomet. Chem.* **1982**, *236*, C28–C30.

(6) Derien, S.; Clinet, J. C.; Dunach, E.; Perichon, J. *Tetrahedron* **1992**, *48*, 5235.

(7) Yoshimura, M.; Nojima, M.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2164.

(8) Brunet, J. J.; Kindela, F. B.; Neibecker, D. *Synth. Commun.* **1989**, *19*, 1923.

(9) Pino, P.; Botteghi, C.; Consiglio, G.; Salomon, C. DE 2359101 June 06, 1974. Using these patent conditions, in our hands, on small scale, 1250 psi syngas pressure ($CO-H_2$ 1:1) was needed to achieve 100% conversion of norbornene in toluene at 100 °C (data not shown).

(10) For a general review, see the hydroformylation reaction: Ojima, I.; Tsai, C.-Y.; Tzamarioudaki, M.; Bonafoux, D. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, 2000; Vol. 56; pp 1−354. For catalytic hydroformylations of α-branched olefins (mostly vinyl compounds), see:(a) Paganelli, S.; Zanchet, M.; Marchetti, M.; Mangano, G. J. *Mol. Catal., A* **2000**, *157*, 1. (b) Alagona, G.; Ghio, C.; Lazzaroni, R.; Settambolo, R. *Organometallics* **2001**, *20*, 5394. (c) Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911. (d) Tijani, J.; El Ali, B. *J. Organomet. Chem.* **2007**, *692*, 3492. (e) Smejkal, T.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 311. (f) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210. (g) Liu, X.; Hu, B.; Fujimoto, K.; Haruta, M.; Tokunaga, M. *Appl. Catal., B* **2009**, *92*, 411.

(11) (a) Van Leeuwen, P. W. N. M.; Roobeek, C. F. *J. Mol. Catal.* **1985**, *31*, 345 (dicyclopentadiene, benzene, 270 psi H_2/CO 2:1, 95 °C, 100% conversion, *exo*/*endo* unknown, 0.2 mol % [$Rh(dppe)_2$]); (b) Parrinello, G.; Deschenaux, R.; Stille, J. K. *J. Org. Chem.* **1986**, *51*, 4189 (norbornylene, benzene, 60 °C, 2625 psi syngas, 100% conv., 87% "selectivity" (yield not determined), *exo* only claimed, 0.23 mol % polystyrene/divinylbenzene polymer-attached [(−)-DBP-DIOP] $PtCl_2-SnCl_2$); (c) Consiglio, G.; Nefkens, S. C. A.; Borer, A. *Organometallics* **1991**, *10*, 2046 (norbornylene, *m*-xylene or benzene, 2325 psi H_2/1050 psi CO, 79% yield, 100% *exo*, 0.1 mol % [(*R*,*R*)-Bco-dpp]$PtCl_2/SnCl_2$); (d) Kollar, L.; Wada, T.; Lautens, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1011 (deltacyclene, toluene, 100 °C, 600 psi syngas, 99% conv., *exo*/*endo* = 93:7, PPh_3-$[Rh(nbd)Cl]_2$ (1.25 mol %) (with 1.25 mol % *S*,*S*-ChiraPhos: 50 °C, 600 psi, 99% conv., *exo*/*endo* = 98:2); (e) Botteghi, C.; Paganelli, S.; Perosa, A.; Lazzaroni, R.; Uccello-Barretta, G. *J. Organomet. Chem.* **1993**, *447*, 153 (norbornylene, toluene, 100 °C, 1500 psi syngas, 98% yield, 100% *exo*, $Pt(C_2H_4)$(dppb) (5 mol %) / CH_3SO_3H); (f) Lu, S.; Li, X.; Wang, A. *Catal. Today* **2000**, *63*, 531 (norbornylene, toluene, 80 °C, 870 psi syngas, 100% yield, carbohydrate-derived synthetic ligand); (g) Lappe, P.; Springer, H.; Lukas, R. DE 10352260 B3, 2005; 0414 (dicyclopentadiene, toluene, 135 °C, 363 psi syngas, 61.3GC-A% monoaldehyde (*exo*/*endo* unknown), Rh-sulfonylated PPh_3 complex). (h) Cossu, S.; Peluso, P.; Alberico, E.; Marchetti, M. *Tetrahedron Lett.* **2006**, *47*, 2569 (norbornadiene system, toluene, 60 °C, 750 psi syngas, $Rh(CO)_2$acac, 30−40% yield); (i) Semeril, D.; Matt, D.; Toupet, L. *Chem.—Eur. J.* **2008**, *14*, 7144; *Adv. Synth. Catal* **2009**, *351*, 1629(norbornylene, H_2O/*n*-decane, 50 °C, 300 psi syngas, 38−93% conv., Rh-acac sulfonylated calixarene ligand, *endo*-aldehyde = main product!).

(12) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, Th.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. *Tetrahedron Lett.* **2005**, *46*, 7831.

(13) Personal communication to T.S. by the manufacturer (Chiral Quest, 7 Deer Park Drive, Suite E, Monmouth Junction, NJ 08852, United States).

(14) The acid **2** obtained by hydroformylation of norbornylene using the commercialized *S*,*S*′,*R*,*R*′-TangPhos ligand was confirmed to be (2*S*)-*exo*-norbornane-2-carboxylic acid (by comparison with the two enantiomers of this acid prepared by an unambiguous method[4]), and ***not*** the (2*R*)-enantiomer as depicted in Scheme 1 of the Amgen publication.[12]

(15) Notably, with calixarene-diphosphite ligands, the rhodium-catalyzed hydroformylation of norbornene leads almost exclusively to the *endo*-isomer; see: Monnereau, L.; Sémeril, D.; Matt, D.; Toupet, L. *Adv. Synth. Catal.* **2009**, *351*, 1629.

(16) Curiously, it had been observed earlier by Andrianary and Jenner that in presence of a cobalt−ruthenium co-catalyst system, tBuOH can participate in hydroformylation reactions via facile formation of the tertiary carbocation, thereby providing a solvent-derived, competent reaction partner (isobutylene) in situ, see: Andrianary, P.; Jenner, G. *J. Organomet. Chem.* **1987**, *322*, 89.

(17) Ruthenium-catalyzed hydroamidation of norbornene using 2-formamidopyridine in a formamide/acetonitrile mixture under pressure (135 °C, autoclave, 1.7 mol % $Ru_3(CO)_{12}$) has been reported to result in a 76% yield (87:13 *exo*/*endo*-mixture) of the aminopyridyl amide of (±)-2-norbornane carboxylic acid, see: Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687.

(18) The X-ray powder diffraction (XRPD) pattern, thermogravimetry (TG) curve and heat−cool cycle differential scanning calorimetry (DSC) curve for the free acid **2** are shown below. The free acid is a low melting (~58 °C) crystalline solid that exhibits a ~10 °C hysteresis of recrystallization upon cooling (5 °C min^{-1}). The TG curve shows that the free acid upon melting will evaporate and even shows some minor sublimation prior to melting (see below). Since the solid is low melting, the free acid may be difficult to crystallize from a reaction solution. Also, drying the material may result in losses due to sublimation.