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Synthesis of Unsaturated Amino Alcohols through Unexpectedly Selective Ru-Catalyzed Cross-Metathesis Reactions†

Hamid R. Hoveyda* and Martin Vézina

Tranzyme Pharma, Inc., Institut de Pharmacologie de Sherbrooke, 3001, 12e Ave Nord, Sherbrooke, Québec J1H 5N4, Canada

hhoveyda@tranzyme.com

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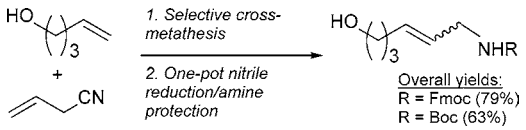
ABSTRACT



A two-step synthesis of N-protected unsaturated amino alcohols is disclosed that relies on an unexpectedly selective cross-metathesis (CM) involving allyl cyanide and pent-4-en-1-ol. The solution concentration and the identity of the Ru complex used are critical to the selectivity and efficiency of CM reactions. The intermediate obtained by CM is converted efficiently to the final desired products through a one-pot nitrile reduction/amine protection procedure.

Effective use of olefin cross-metathesis (CM)[1] in a synthetic strategy requires addressing the problem of product selectivity so as to obtain the desired product in a higher yield than the material formed through homodimerization processes.[2] Since Crowe's pioneering investigations a decade ago,[3] several examples of selective Mo- and Ru-catalyzed CM have appeared in the literature.[1] Nonetheless, applications of catalytic CM remain limited in scope, since complications related to the issue of pair selectivity are not yet fully resolved.

In principle, product selectivity in catalytic CM can be controlled by juxtaposition of olefin partners such that any homodimerization proceeds more slowly than the desired transformation involving the olefin cross partners.[2a,16] In a number of studies, steric and electronic attributes of CM partners, together with the choice of an optimal catalyst, have been exploited to achieve high selectivity.[1] In the context of a predictive model for catalytic CM selectivity, Grubbs and co-workers have recently proposed a categorization of olefins according to relative rates of homodimerization and as a function of the type of metathesis catalyst used.[4] Consequently, olefins were divided into four categories, ranging from Type I (those that readily undergo homodimerization)

† Dedicated to the memory of our late colleague, Mr. John Dwyer.

(1) For recent general reviews on CM, see: (a) Chatterjee, A. K. In *Handbook of Metathesis*; Grubbs, R. H, Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, Chapter 2.8, pp 246−295. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

(2) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370 and references therein. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58−71. Lack of control over *E*/*Z* stereoselectivity is an additional problem in catalytic CM reactions. As noted in ref 2a, a further complication is that product selectivity and stereoselectivity are influenced by one another as a result of secondary metathesis reactions.

(3) (a) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998−10999. (b) Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162−5163. (c) Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117−2120. Schrock's Mo complex, Mo(=CHCMe$_2$Ph)(=NAr)[OCMe(CF$_3$)$_2$]$_2$ (Ar = 2,6-*i*-Pr$_2$C$_6$H$_3$), **4**, was employed in these early studies.

(4) Only Ru complexes **1** and **2** and Mo complex **4** were included in their report (cf. ref 2a).

(5) Ru-catalyzed CM with N-protected allylamine (Type I) is not a viable option due to conversion to enamines. See: (a) Toste, F. D.; Chatterjee, A. K.; Grubbs, R. H. *Pure Appl. Chem.* **2002**, *74*, 7−10. (b) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839−1841. Other related amines cannot be purchased. Attempts to effect CM between protected allylamine and Type I hydroxy-olefins (e.g., **5c** and its trityl-protected form), with **2** or **3**, failed in our hands. The cross product was detected (by ^{1}H NMR) in ≤5% after partial purification.

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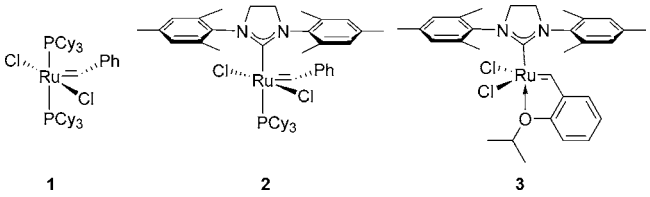
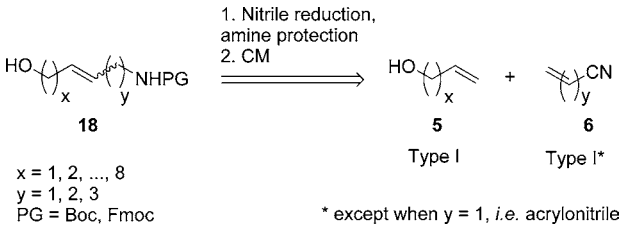


Figure 1. Grubbs **1** and **2** and Hoveyda−Grubbs **3** Ru complexes.

to Type IV (entirely unreactive toward catalytic CM). On the basis of this categorization, catalytic CM between two Type I olefins would be expected to engender a statistical mixture of products (e.g., 66% CM product yield when a 2:1 mixture of cross partners is used).

In connection with a medicinal chemistry program, we recently required a facile synthetic route that would provide rapid access to a range of unsaturated amino alcohols of the type represented by **18** in Scheme 1. To this end, we set out to determine the scope of catalytic CM strategy, as outlined in Scheme 1.[5] This decision was made despite the aforementioned proposal by Grubbs suggesting that matching two

Scheme 1. Retrosynthesis of Unsaturated Amino Alcohols through CM

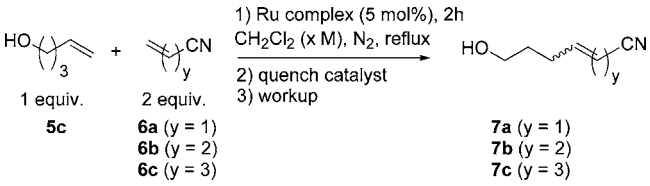


Type I CM partners should not be conducive to high product selectivity.

Herein we present the results of our studies aimed toward synthesis of compounds **18** through Ru-catalyzed CM reactions. In the course of these investigations, we made a number of unexpected observations related to factors that govern the facility and selectivity of catalytic CM reactions. These observations and their potential implications are disclosed.

The data regarding the screening of Ru complexes (**1**−**3**) in the CM reaction involving pent-4-en-1-ol (**5c**) in the presence of acrylonitirle (**6a**), allyl cyanide (**6b**), or homoallyl cyanide (**6c**) are summarized in Table 1. Of the three CM

Table 1. Screening of the Catalytic Activity of **1**−**3**, and the Effect of Reaction Concentration on Ru-Catalyzed CM[a]



entry	Ru complex	reaction concentration (M)	product, yield (%),[b] *E*:*Z* ratio[c]
1[d]	**2**	0.5	**7a**, 35, 1:2
2[d]	**3**	0.07	**7a**, 74, 1:2.5
3[d]	**3**	0.24	**7a**, 60, 1:2
4	**1**	1.2	**7b**, 2, 3.5:1
5	**2**	0.05	**7b**, 38, 6:1
6	**2**	0.5	**7b**, 81, 6:1
7	**3**	0.05	**7b**, 72, 2:1
8	**3**	0.5	**7b**, 65, 6:1
9	**2**	0.5	**7c**, 72, 5:1[e]
10	**3**	0.05	**7c**, 48, 4:1[e]

[a] Other reaction parameters were optimized separately. All reactions were conducted using 5.8 mmol of alcohol substrate. [b] Yields are based on the isolated, purified products. [c] *E*:*Z* ratios were determined by ^{1}H NMR. [d] Reaction time = 3 h. [e] Due to signal overlap in ^{1}H NMR, the *E*:*Z* ratios were based on ^{13}C NMR data.

partners (**6a**−**c**), only the electron-deficient acrylonitrile (**6a**) has been previously reported to afford good product selectivity, presumably due to its slow rate of homodimerization.[6] Furthermore, the higher reactivity of phosphine-free

(6) Acrylonitrile is absent from Grubbs' olefin categorization with **1** and **2** (cf. ref 2a). Given the reluctance of acrylonitrile to undergo homodimerization, it is perhaps best to categorize this alkene as a Type III with **3** and as a Type IV with complexes **1** or **2**.

(7) (a) For a review of Hoveyda−Grubbs Ru catalysts, see: Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biol. Chem.* **2004**, *2*, 8−23 and references therein. (b) A study of CM reaction using **3** and involving unsaturated alcohols was reported by: Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327−332. (c) For a phosphine-free variant of **2** that effects CM of acrylonitrile; see: Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035−4037.

(8) (a) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001** 430−432. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976.

(9) For reports describing the attempted use of allyl cyanide in CM reactions, see: (a) Giger, T.; Wigger, M.; Audétat, S.; Benner, S. A. *Synlett* **1998**, 688−691. (b) BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465−3467. No CM product was obtained with **1** (ref 9a). (Thus, allyl cyanide might be considered as a Type IV olefin with **1**; cf. Table 1, entry 4.) In the example described in ref 9b, a substatistical yield of 23% was obtained with **3**, and this low yield was attributed to the "presence of a cyano group".

(10) (a) Homodimers of **5c** (7% isolated yield) and **6b** (5%) (Table 1, entry 6) were generated as side-products. Moreover, when this reaction was conducted using 1.1 equiv of allyl cyanide, **7b** was obtained in 72% yield and homodimers **5c** and **6b** were isolated in 7 and 11% isolated yields, respectively. (b) For a study on the impact of concentration in RCM, see: Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297−3299.

(11) Conditions shown for synthesis of **7c** were not fully optimized.

(12) As discussed in ref 2a, the higher quantities of the thermodynamically favored *E* isomer may be a reflection of the comparative ability of **7a** and **7b** to undergo *E*/*Z* isomerization through secondary metathesis processes.

(13) Conditions refined for **7b** (Table 1, entry 6) may not be optimal for these other substrates (in Table 2). Nevertheless, inasmuch as the general trends reveal, the results in Table 2 aid in demarcating the scope of CM reactions with allyl cyanide.

(14) The desired CM product (Table 2, entry 3) coeluted with the homodimer of allyl cyanide (~12%) as characterized by NMR (^{1}H, ^{13}C).

(15) Conducting CM reaction with **10** for 16 h, a duration comparable to that used in ref 2a, resulted in a similar yield of 24%. The homodimer of **10** was the major side-product isolated (24% yield); the homodimer of allyl cyanide (**6b**) was also obtained in <2% yield.

(16) As expected, matching Type I/II cross partners resulted in slightly improved CM selectivity (cf. Table 2, entries 1 vs 6).

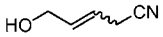
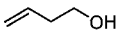
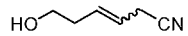
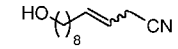
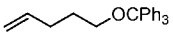
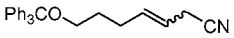
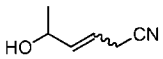
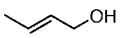
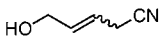
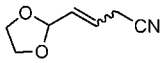
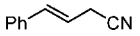
Hoveyda−Grubbs Ru complex[7] (**3**) toward such electron-deficient substrates is well recognized (cf. Table 1, entries 1−3).[8] The results illustrated in Table 1 indicate that, in addition to **6a**, unsaturated nitriles ***6b*** *and* ***6c*** *can be effective cross partners with certain Type I olefin partners provided that the reaction concentration is optimized.* Contrary to CM reactions involving acrylonitrile, to the best of our knowledge, neither allyl cyanide (**6b**) nor homoallyl cyanide (**6c**) have been reported as effective cross partners thus far.[9]

The critical effect of reaction concentration is illustrated by the observation that the yield of product **7b** with Ru complex **2** is nearly doubled to ∼80% when a 0.5 M solution is used (vs a 0.05 M solution; Table 1, entries 5−6).[10] Such modifications of the reaction conditions allowed us to prepare substantial amounts of CM products in a reliable fashion. Thus, when the catalytic CM shown in entry 6 of Table 1 was carried out in a 5 g scale process, the desired product **7b** was isolated in 75% yield (unoptimized) after purification. It should be noted that when Ru complex **3** was used for the same reaction (Table 1, entry 6), the trend regarding solution concentration did not hold; instead, a similar or slightly lower yield of the desired CM product was obtained upon concentrating the reaction mixture (Table 1, entries 7 and 8). As illustrated in entry 9 of Table 1, in catalytic CM involving homoallyl cyanide **6c**, a 0.5 M solution used in reactions involving Ru complex **2** afforded high product selectivity (Table 1, entry 9).[11] Enhancement of the CM product selectivity through control of a simple parameter (solution concentration) again proved to be sufficient to allow us to employ the strategy shown in Scheme 1 by preparing multigram quantities of the intermediate **7b** through Ru-catalyzed CM. Finally, regarding the data summarized in Table 1, it should be noted that Ru-catalyzed CM reaction with allyl cyanide proceeded with greater (and opposite) stereoselectivity ($E/Z \geq 6{:}1$) than that typically obtained with acrylonitrile ($E/Z \leq 1{:}3$) (cf. Tables 1 and 2).[12]

With the above encouraging results in hand, we carried out additional experiments to define the scope and limitations of these findings. Thus, catalytic CM reactions between allyl cyanide and several other Type I and II olefins were conducted under the optimized conditions in the presence of Ru complex **2** (cf. Table 1, entry 6).[13] Among hydroxylated terminal olefin partners examined, only homoallylic alcohol **5b** underwent selective CM with **6b** (77% yield) (Table 2, entry 2); reaction of allyl alcohol (**5a**) and dec-9-en-1-ol (**5d**) proved to be significantly less efficient (Table 2, entries 1 and 3). Interestingly, it was observed that *O*-trityl protection of pen-4-en-1-ol adversely affects product selectivity (cf. 23% yield, Table 2, entry 4 vs 81% yield, Table 1, entry 6).

On the other hand, matching allyl cyanide against Type II hydroxy-olefin partners such as a secondary allylic alcohol (**10**, Table 2, entry 5) or a disubstituted allylic alcohol (**12**, entry 6), resulted in substatistical product yields (21%, Table 2, entry 5[15] and 46%, Table 2, entry 6[16]). Catalytic CM of vinyl dioxolane **13** (Table 2, entry 7), considered a Type II partner, proceeded similarly (26% yield). Collectively, the above observations suggest that in Ru-catalyzed CM reactions between allyl cyanide and terminal hydroxy-olefin substrates, formation of transient five- or six-membered hydroxy-alkylidene Ru chelates may serve to enhance product selectivity significantly.[17]

Table 2. Ru-Catalyzed CM between Allyl Cyanide and Type I and Type II Olefins Promoted by Ru Complex **2**[a]

entry	CM partner	product, yield (%),[b] (*E*/*Z* ratio)[c]
1	 **5a** (Type I)	 **7d**, 38, (15:1)
2	 **5b** (Type I)	 **7e**, 77, (3.5:1)
3	 **5d** (Type I)	 ~16,[d] (2.5:1)
4	 **8** (Type I)	 **9**, 23, (2.5:1)
5	 **10** (Type II)	 **11**, 21, (5:1)
6	 **12** (Type II)	 **7d**, 46, (15:1)
7	 **13** (Type II)	 **14**, 26, (2.5:1)
8	 **15** (Type I)	 **16**, 10, (only *E* detected)

[a] Reaction conditions: allyl cyanide (2 equiv), CM partner (1 equiv), Ru complex **2** (5 mol %), CH_2Cl_2, reflux, [reaction] = 0.5 M, 2 h. [b] Yields are based on isolated purified products. [c] *E*:*Z* ratios were determined by ^{1}H NMR. [d] Percent conversion for this entry was determined by ^{1}H NMR after partial purification.[14]

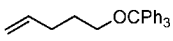
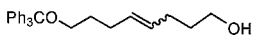
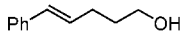
Two further experiments were performed using pent-4-en-1-ol (**5c**) as the cross partner with either its *O*-trityl-protected form **8** or with styrene[18] (Table 3). In both cases, product yields were below the anticipated 66% statistical yield for the 1:2 stoichiometry employed. Thus, the potential Ru-oxygen chelation alone is not sufficient to rationalize the unexpectedly high CM product selectivity obtained in the foregoing studies with pent-4-en-1-ol (**5c**).

A few comments on the workup following the CM reaction are noteworthy. To minimize secondary metathesis processes that can adversely affect the yield and purity during the

(17) For studies on chelation effects in CM, see: (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451−1454. (b) Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209−2212. (c) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274. (d) For the effect of free allylic hydroxyl group on the RCM reaction rates, see: Hoye, T. R.; Zhao, H. *Org. Lett.* **1999,** *1*, 1123−1125.

(18) In addition to the CM product (Table 3, entry 2), a side-product that tenaciously coeluted was also detected (∼15%) and was characterized as Ph-CH═CH−$(CH_2)_2$−OH (^{1}H−^{1}H COSY, GC-MS). This adventitious product is likely the result of olefin isomerization (in **5c**) followed by CM. For other related examples, see: Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1259−1262 and references therein.

Table 3. Ru-Catalyzed Cross-Metathesis Reactions Involving Pent-4-en-1-ol (**5c**) Promoted by Ru Complex **2**[a]

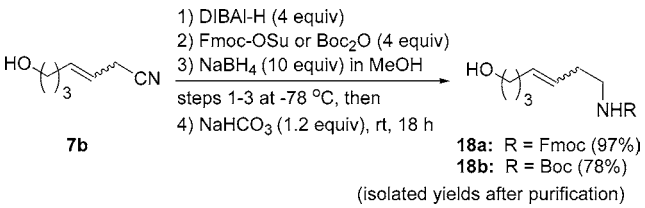
entry	CM partner	product, yield (%), (*E*/*Z* ratio)
1	 **8** (Type I)	 **17**, 60%,[b] (2.5:1)[c]
2	 (Type I)	 ~20%,[d] (only *E* detected)[e]

[a] Reaction conditions: pen-4-en-1-ol (1 equiv), CM partner (2 equiv), Ru complex **2** (5 mol %), CH_2Cl_2, reflux, [reaction] = 0.5 M, 2 h. [b] Isolated yield after purification. [c] Due to signal overlap in ^{1}H NMR, the *E*:*Z* ratio was based on ^{13}C NMR data. [d] Percent conversion for this entry was determined by ^{1}H NMR after partial purification.[17] [e] Based on ^{1}H NMR data.

workup, any remaining catalyst was quenched with ~50 equiv of ethyl vinyl ether,[19] added together with ~50 equiv of DMSO upon completion of reaction. Addition of DMSO facilitates removal of colored Ru impurities in the subsequent purification steps.[20] After addition of the above reagents and stirring for 1 h in air, the mixture was concentrated in vacuo.[21] Purification by silica gel flash chromatography afforded product samples with trace Ru levels (<0.1%, ICP-ES) irrespective as to whether Ru complex **2** or **3** was employed.

The nitrile intermediate **7b** furnished by CM was subjected to the synthesis route shown in Scheme 2 to carry out both the chemoselective reduction of nitrile moiety and the protection of the resultant primary amine by a one-pot procedure. Other procedures attempted either suffered from lack of adequate chemoselectivity[22] or resulted in the formation of a secondary amine dimeric side-product[23] that not only lowered the yield but also rendered the purification arduous.[24]

Scheme 2. One-Pot Nitrile Reduction/Amine Protection Procedure



In conclusion, we have observed that reaction concentration, as a function of the type of Ru complex used, can be a critical experimental parameter in controlling product selectivity in Ru-catalyzed CM reactions. Selective CM reactions between allyl cyanide and several terminal hydroxy-olefins were thus achieved. Such considerations should prove to be useful in future studies regarding synthesis of olefins through metal-catalyzed CM transformations. Finally, the nitrile intermediates obtained through catalytic CM rendered feasible a succinct synthesis of unsaturated amino alcohols upon effecting nitrile reduction chemoselectively.

Supporting Information Available: Experimental procedures and full characterization of compounds **7a**−**e**, **8**, **9**, **11**, **14**, and **16**−**18** and ICP-ES data for % Ru content (**7b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6453−6554.

(20) Ahn Y. M.; Yang, K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411−1413.

(21) This crude residue was immediately passed through a short silica gel column (EtOAc/hexanes 3:1) to remove the bulk of the colored impurity. The final purification can be postponed, if necessary.

(22) Cimino, G.; Gavagnin, M.; Sodano, G.; Spinella, A.; Strazzullo, G.; Schmitz, F.; Yalamanchili, G. *J. Org. Chem.* **1987**, *52*, 2301−2303.

(23) (a) Using conditions reported in: Dolle, R. E.; Nicolaou *J. Am. Chem. Soc.* **1985**, *107*, 1691−1694. Gallagher, T. F.; Adams, J. L. *J. Org. Chem.* **1992**, *57*, 3347−3353. (b) This side-reaction ensues when the attack of the primary amine onto the intermediate imine proceeds more rapidly than the corresponding hydride attack. See: Gould, F. E.; Johnson, G. S.; Ferris, A. F. *J. Org. Chem.* **1960**, *25*, 1658−1660. Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1995**, *26*, 6413−6416. Caddick, S.; Haynes, A. K. de K.; Judd, D. B.; Williams, M. R. V. *Tetrahedron Lett.* **2000**, *41*, 3513−3516.

(24) Other strategies to suppress this side-product include: (i) use of nickel or cobalt boride (catalytic) with excess $NaBH_4$ (cf.: Ganem, B.; Osby, J. O. *Chem Rev.* **1986**, *86*, 763−780 and references therein) and (ii) a variant of strategy i, whereby the protection of the primary amine group is effected in a one-pot manner; however, this procedure, in contrast to that in Scheme 2, fully reduces conjugated nitrile moieties (cf. entries 14 and 15 in: Caddick, S.; Judd, D. B.; Lewis, A. K. de K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417−5423).