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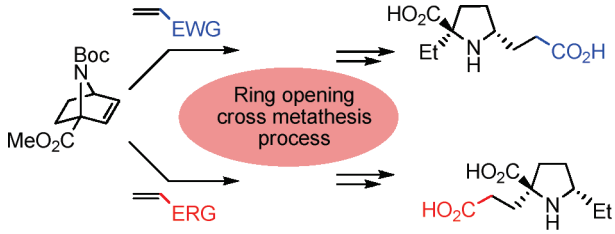
A Highly Regioselective Ring-Opening Metathesis−Cross Metathesis Process Modulated by the Electronic Effects of the Cross Metathesis Partner: An Entry to Quaternary Prolines

Javier Carreras, Alberto Avenoza,* Jesús H. Busto,* and Jesús M. Peregrina

Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, UA-CSIC, 26006 Logroño, Spain

alberto.avenoza@unirioja.es; hector.busto@unirioja.es

Received October 27, 2008



A modulation of the regioselectivity in the ring-opening metathesis−cross metathesis (ROCM) process, originated by the electronic features of the acyclic olefin, is described. Electron-poor and electron-rich olefins showed opposing behavior giving different regioisomers. The reaction opens the way to the synthesis of interesting proline analogues incorporating a quaternary stereocenter.

Tandem catalytic metathesis reactions have appeared in recent times as a powerful tool for the construction of complex organic molecules.[1] In this context, the ring-opening cross metathesis (ROM-CM or ROCM) reactions allow the construction of complex ring systems.[2] The ROCM reactions of norbornene or oxanorbornene derivatives have received a great deal of attention because they represent a powerful entry for the synthesis of highly substituted five- and six-membered rings.[3] The use of azanorbornenes in ROCM reactions allows the synthesis of interesting polysubstituted pyrrolidines and piperidines.[4] Because of this, the 7-azanorbornene systems have been the subject of recent papers.[5] Thus, when unsymmetrical bicyclic olefins are used, the control of the regioselectivity of ROCM reactions is crucial and little attention is centered on the influence of bridgehead substituent.[6] In this regard, understanding the steric and electronic forces that guide the regioselectivity is an important challenge in advancing these intermolecular transformations to their fullest potential.

As a part of our research project on the chemistry of azanorbornanes,[7] we have developed the ROCM reaction of methyl *N*-Boc-7-azabicyclo[2.2.1]hept-2-en-1-carboxylate (**1**) to study the metathesis reaction in bridgehead-substituted systems. In particular, we focused our interest on the participation of olefins with electron-withdrawing groups (EWG), such as methyl acrylate (Table 1, entry 1), in the CM process, which occurred with an excellent yield and regioselectivity. As catalysts, we used second-generation Grubbs (G) and second-generation Hoveyda−Grubbs (H−G) to obtain only one regioisomer in both cases. However, with the latter, we obtained the best yield (98% vs 76%). This reaction opened the way to obtain the amino diacid **2** (Figure 1).[8] It is important to notice that there are few examples in which the ROCM process occurs in a highly regioselective fashion; therefore, in order to understand this behavior, we wish to extend the reactivity of 7-azabicyclic compound **1** to other olefins (Table 1).

When we attempted the metathesis reaction with styrene (Table 1, entry 4), the best conditions involved the use of second-generation Grubbs catalyst at 55 °C to give in 82% yield a mixture of the *E* and *Z* stereoisomers of the two possible

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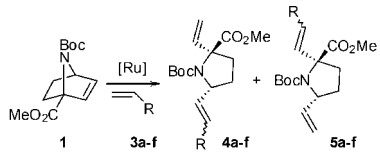
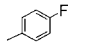
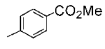
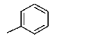
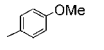
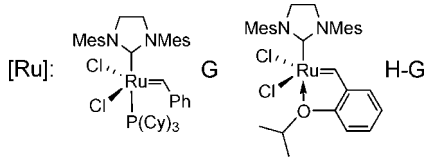
10.1021/jo802399k CCC: $40.75
Published on Web 01/09/2009

TABLE 1. Modulation of the Regioselectivity in the ROCM Process



entry	R	olefin[a]	[Ru][b]	solvent	T (°C)	4a-f/5a-f[c] (yield, %)
1	CO_2Me	**3a**	H-G	$PhCH_3$	80	100/0 (98)
2		**3b**	G	$CHCl_3$	55	67/33 (81)
3		**3c**	G	$CHCl_3$	55	48/52 (71)
4		**3d**	G	$CHCl_3$	55	36/64 (82)
5		**3e**	G	$CHCl_3$	55	22/78 (79)
6	SPh	**3f**	G	$CHCl_3$	55	0/100 (89)

[a] Four equivalents of olefin were added. [b] G, second-generation Grubbs catalyst; H−G, second-generation Hoveyda−Grubbs catalyst; 0.08 equiv was added. [c] Reaction followed by GC-MS, yield obtained from isolated product after column chromatography and ratio measured by derivatization using ^1H NMR for all entries (see Scheme 2) and HPLC for entries 4 and 5 (see Supporting Information).



regioisomers **4d** and **5d**. To eliminate this complex mixture and avoid the Boc rotamers, we decided to carry out the hydrogenation using hydrogen with Pd−C as a catalyst and subsequent hydrolysis of the Boc group with TFA (Scheme 1). In this way and using a TOCSY experiment to identify the corresponding regioisomers, we could evaluate the ratio of these isomers (36:64). Remarkably, the major regiosiomer **5d** was the opposite of that using methyl acrylate as an acyclic olefin.

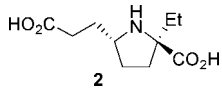
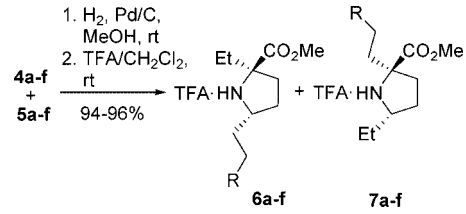


FIGURE 1. Amino diacid obtained using ROCM of **1** and methyl acrylate.

To understand this feature and taking into account that the increase of the steric effects in the ROCM process with acrylates gave the same regioisomer,[8] we addressed the subject of electronic effects. Therefore, we attempted the ROCM reaction using styrene derivatives with different substitution at the *para* position of the aromatic ring. For each case, the mixture of regioisomers was treated under the same procedure above-described (hydrogenation and subsequent hydrolysis of the Boc group, Scheme 1). When the substitution in the *para* position provided an electron-withdrawing feature to the olefin (F and CO_2Me substituents), we obtained the compound **4b** as major regioisomer in a 67:33 ratio for the fluor case (Table 1, entry 2) and a similar ratio of regioisomers **4c** and **5c** for CO_2Me group (Table 1, entry 3). When more character-donating nature is present (OMe substituent), the ratio of regioisomers (22:78) increased in favor of regioisomer **5e** (Table 1, entry 5). We could

SCHEME 1. Hydrogenation and Subsequent Hydrolysis of the Boc Group



observe a good correlation between the electronic features of the acyclic olefins and the ratio of regioisomers (Figure 2).

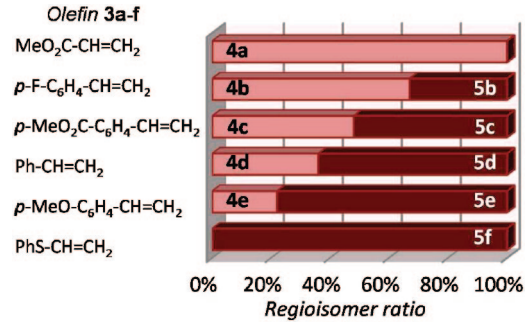
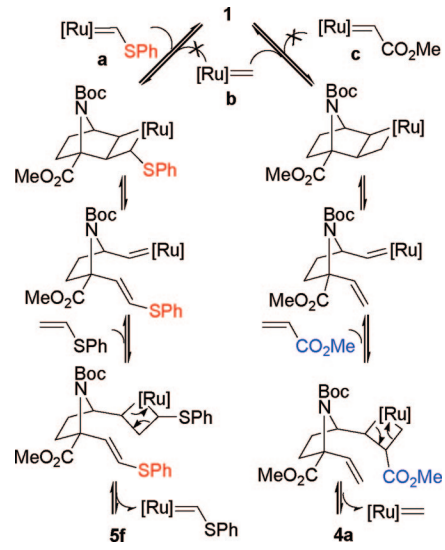


FIGURE 2. Correlation between acyclic olefins and regioisomer ratio.

Definitively, when we used an olefin with an electron-releasing group (ERG), such as phenylvinylthioether, the reaction was carried out in an excellent yield (89%), thus providing a single regioisomer **5f**. Figure 2 also shows the correspondence between this olefin and the regioisomer ratio obtained, which at least qualitatively agrees with the expected tendency.

Taking into account that the bicyclic olefin **1** is the same in all entries of Table 1 and that the size of cross metathesis partner does not appear to influence the regioselectivity,[8] we suspect that an electronic effect related to the stability of ruthenium carbenes (**a**, **b**, **c** in Scheme 2) is involved in the regioselectivity.[2f] Therefore, we propose the formation of metallacyclobutane intermediates with the ruthenium on the opposite side of the methyl ester group, in order to minimize the steric

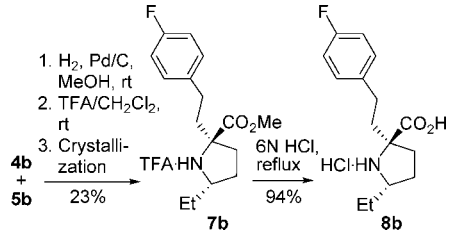
SCHEME 2. Selectivity Model for ROCM Processes



effect.[3b] In the case of olefins with electron-withdrawing groups such as **3a**, the results of the reaction suggest that the ruthenium methylidene intermediate (**b**) is the propagating specie, due to the low stability of the metal alkylidene carbine (**c**).[2i] When an electron-releasing group was incorporated in the olefin (**3f**), the propagating ruthenium alkylidene (**a**)[3d,f] could be responsible for the reaction (Scheme 2).

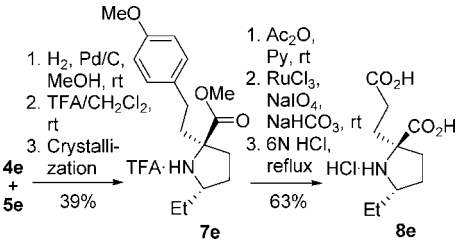
To show the synthetic applicability of this tandem reaction, we obtained interesting quaternary amino acids.[9] Therefore, in the case of mixture **4b** and **5b**, after the corresponding hydrogenation and subsequent hydrolysis of the Boc group, compound **7b** was purified by slow crystallization. The X-ray diffraction of monocrystals of this compound confirmed the stereochemistry deduced by NMR experiments (see Supporting Information). The hydrolysis of the methyl ester group gave the restricted amino acid **8b**, which can be regarded as a quaternary proline with the attractive feature of incorporating a fluorine atom in its structure (Scheme 3).

SCHEME 3. Synthesis of the Quaternary Proline Analogue 8b



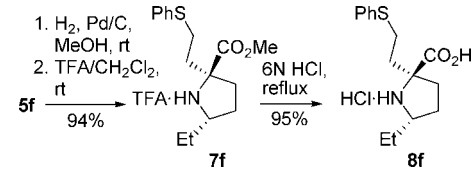
The same procedure above-described was carried out with an isomeric mixture of **4e** and **5e**, allowing us to obtain, after hydrogenation, hydrolysis of the Boc group, and slow crystallization, the compound **7e**. Protection of the amino group and subsequent oxidation of the *p*-methoxybenzene group with RuO_4, followed by the hydrolysis of the methyl ester group, gave the 2-(2-carboxyethyl)-5-ethylpyrrolidine-2-carboxylic acid structure (**8e**), which merges the proline and the glutamic acid substructures (Scheme 4). The combination of both skeletons has attracted the attention of the synthetic chemist, since they are present in several biologically active compounds (e.g., kaitocephalin,[10] kainic acid,[11] domoic acid,[11] and 3-prolinoglutamic acid[12]).

SCHEME 4. Synthesis of the Quaternary Proline Analogue 8e



The single regioisomer **5f**, obtained from phenylvinylthioether olefin, was hydrogenated, and after removing the Boc group, we obtained the compound **7f** in an excellent yield. The structure of this compound was unambiguously determined by X-ray diffraction (see Supporting Information). The final hydrolysis of the methyl ester group allowed us to obtain the amino acid **8f**, a chimera of proline and *S*-phenylhomocysteine (Scheme 5).

SCHEME 5. Synthesis of the Quaternary Proline Analogue 8f



In conclusion, we have studied a regioselective ROCM process between compound **1**, a bridgehead-substituted 7-azanorbornene, and several olefins. Electron-poor and electron-rich olefins showed different behavior, giving different regioisomers. Thus, the regioselectivity of the ROCM process could be modulated by the electronic effect of the substituent in the acyclic olefin. This tandem reaction opens the way to obtain interesting quaternary amino acids, some of which are chimera structures of proline and glutamic acid.

Experimental Section

General Procedure for the ROCM Process. To a solution of azabicycle **1** (180 mg, 0.71 mmol) in the corresponding solvent (14 mL, Table 1) were added Grubbs second-generation catalyst (24 mg, 0.03 mmol) and acyclic olefin **3b**−**f** (1.42 mmol). The reaction mixture was stirred at the corresponding temperature for 16 h, then a second portion of catalyst (24 mg, 0.03 mmol) and acyclic olefin (1.42 mmol) were added, and the reaction was stirred for another 8 h. The solvent was evaporated to obtain, after column chromatography (hexane/ethyl acetate, 8:2), a mixture of regioisomers **4b**−**f** and **5b**−**f**.

Synthesis of Amino Acid 8b. A solution of the mixture of **4b** and **5b** (214 mg, 0.57 mmol) in degassed MeOH (6 mL) was added over a suspension of 10% Pd/C (76 mg) in degassed MeOH (12 mL). The compounds were hydrogenated at room temperature and atmospheric pressure overnight. The reaction mixture was filtered over celite and evaporated to obtain a colorless oil. To a solution of this crude in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (0.5 mL). The reaction mixture was stirred at room temperature for 4 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 208 mg of an oily mixture of **6b** and **7b** (78% from **1** in 3 steps) as trifluoroacetic salts. Once crystallized from a mixture of hexane/CH_2Cl_2, compound **7b** (35 mg, 0.13 mmol) was suspended in an aqueous 6 N HCl solution (4 mL) and heated under reflux for 17 h. The solvent was evaporated in vacuo. Purification of the residue with a C18 reverse-phase sep-pack cartridge gave 25 mg (94%) of the corresponding amino acid as the solid hydrochloride derivative **8b** (18% from **1** using four steps). Mp: 138−9 °C. Anal. Calcd for $C_{15}H_{21}ClFNO_2$: C, 59.70; H, 7.01; N, 4.64. Found: C, 59.63; H, 7.05; N, 4.59. Exact mass for ($C_{15}H_{21}FNO_2^+$, ESI+): (calcd) 266.16, (found) 266.2. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 0.97 (t, 3H, CH_3, J = 7.5 Hz), 1.67−1.90 (m, 3H), 2.08−2.26 (m, 3H), 2.34−2.43 (m, 1H), 2.45−2.59 (m, 2H), 2.65−2.74 (m, 1H), 3.62−3.71 (m, 1H), 6.99−7.10 (m, 2H), 7.19−7.28 (m, 2H). ^{13}C NMR (100 MHz, D_2O) δ (ppm): 12.8, 27.7, 30.3, 32.1, 36.6, 39.7, 65.7, 75.3, 117.8 (d, J = 21.4 Hz), 132.5 (d, J = 8.1 Hz), 138.2 (d, J = 3.0 Hz), 163.9 (d, J = 241.6 Hz), 175.9.

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Synthesis of Amino Diacid 8e. A solution of the mixture of **4e** and **5e** (216 mg, 0.56 mmol) in degassed MeOH (6 mL) was added over a suspension of 10% Pd/C (73 mg) in degassed MeOH (12 mL). The compounds were hydrogenated at room temperature and atmospheric pressure overnight. The reaction mixture was filtered over celite and evaporated to obtain a colorless oil. To a solution of this crude in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (0.5 mL). The reaction mixture was stirred at room temperature for 3 h, and the solvent was removed. The residue was solved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 206 mg of an oily mixture of **6e** and **7e** (75% from **1** in 3 steps) as trifluoroacetic salts. Once crystallized from a mixture of Et_2O/CH_2Cl_2, compound **7e** (85 mg, 0.29 mmol) was solved in pyridine (4 mL), and acetic anhydride was added (2 mL). After stirring for 7 h, the solvent was removed, and the residue was dissolved in toluene (2 × 5 mL) and then evaporated. The resulting compound was purified by silica gel column chromatography eluting with hexane/EtOAc (3:7) to give the corresponding amide (60 mg, 82%). A solution of $NaIO_4$ (284 mg, 1.33 mmol) in H_2O (16 mL) was treated with a solution of the above amide in $EtOAc/CH_3CN$ (1:1, 4 mL) followed by $RuCl_3 \cdot H_2O$ (1.6 mg, 0.01 mmol) and $NaHCO_3$ (24 mg). The reaction mixture was stirred at 30 °C for 4 d. After this time, it was extracted with saturated aqueous $NaHCO_3$ (20 mL) and washed with CH_2Cl_2. The aqueous layer was acidified with 2 N HCl to pH 2−3 and extracted with EtOAc (3 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo to provide the carboxylic acid derivative (41 mg, 84%). This acid was suspended in an aqueous 6 N HCl solution (5 mL) and heated under reflux for 16 h. After evaporation of the solvent, the residue was purified with a C18 reverse-phase sep-pack cartridge to give 35 mg (92%) of the corresponding amino acid as an oily hydrochloride derivative **8e** (20% from **1** using six steps). Anal. Calcd for $C_{10}H_{18}ClNO_4$: C, 47.72; H, 7.21; N, 5.56. Found: C, 47.79; H, 7.31; N, 5.48. ^{1}H NMR (400 MHz, D_2O) δ (ppm): 1.00 (t, 3H, J = 7.3 Hz), 1.68−1.89 (m, 3H), 2.12−2.32 (m, 3H), 2.38−2.46 (m, 1H), 2.49−2.57 (m, 3H), 3.65−3.73 (m, 1H). ^{13}C NMR (100 MHz, D_2O) δ (ppm): 12.8, 27.7, 30.5, 31.9, 32.8, 36.3, 65.6, 74.9, 175.9, 178.7.

Synthesis of Amino Acid 8f. A solution of **5f** (280 mg, 0.72 mmol) in degassed MeOH (8 mL) was added over a suspension of 10% Pd/C (300 mg) in degassed MeOH (12 mL). The compound was hydrogenated at room temperature and atmospheric pressure overnight stirring. The reaction mixture was filtered over celite and evaporated to obtain 278 mg (99%) of a yellow oil. To a solution of 40 mg of this compound in CH_2Cl_2 (10 mL) was added trifuoroacetic acid (0.5 mL) was added. The reaction mixture was stirred at room temperature for 3 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (10 mL) and then evaporated. This operation was repeated several times to obtain 37 mg (95%) of a white solid corresponding to compound **7f**, as a trifluoroacetic salt. Compound **7f** (50 mg, 0.17 mmol) was suspended in an aqueous 6 N HCl solution (5 mL) and heated under reflux for 17 h. The solvent was evaporated in vacuo. Purification of the residue with a C18 reverse-phase sep-pack cartridge gave 38 mg (95%) of the corresponding amino acid as the solid hydrochloride derivative **8f** (89% from **1** using four steps). Mp: 216−7 °C. Anal. Calcd for $C_{15}H_{22}ClNO_2S$: C, 57.04; H, 7.02; N, 4.43. Found: C, 57.12; H, 7.10; N, 4.48. Exact mass for ($C_{15}H_{22}NO_2S^+$, ESI+): (calcd) 280.14, (found) 280.4. ^{1}H NMR (400 MHz, D_2O/CD_3OD) δ (ppm): 1.04 (t, 3H, J = 7.5 Hz), 1.63−1.78 (m, 2H), 1.80−1.92 (m, 1H), 1.98−2.08 (m, 1H), 2.12−2.25 (m, 2H), 2.35−2.56 (m, 2H), 2.87−3.03 (m, 2H), 3.56−3.67 (m, 1H), 7.18−7.25 (m, 1H), 7.28−7.39 (m, 4H). ^{13}C NMR (100 MHz, D_2O/CD_3OD) δ (ppm): 11.3, 26.6, 29.2, 29.7, 35.2, 37.3, 64.0, 74.3, 127.6, 130.2, 130.7, 136.6, 173.6.

Acknowledgment. We thank the Ministerio de Ciencia e Innovación and FEDER (project CTQ2006-05825/BQU), the Universidad de La Rioja (EGI08/06), and the Gobierno de La Rioja (grant for J.C.).

Supporting Information Available: Experimental details, spectroscopic characterization of all compounds, crystal structure data in CIF format, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802399K