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COMMUNICATION

Modular synthesis of optically active lactones by Ru-catalyzed asymmetric allylic carboxylation and ring-closing metathesis reaction†

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Received 29th December 2011, Accepted 27th February 2012
DOI: 10.1039/c2cc18137a

A new synthetic route to optically active unsaturated γ- and δ-lactones has been demonstrated *via* asymmetric allylic carboxylation with a planar-chiral Cp′Ru catalyst and ring-closing metathesis reaction with a Grubbs II catalyst, and successfully applied to the enantioselective synthesis of (*R*)-(−)-massoialactone.

Optically active lactones constitute a structural motif shared by many natural products and biologically relevant molecules.[1] The efficient synthesis of such molecules remains an exciting challenge in organic chemistry even though a number of ingenious reactions have been developed by utilizing metal catalysts[2] and organocatalysts[3] in the last decade. The ring-closing metathesis reaction (RCM) is a powerful tool for the synthesis of cyclic compounds[4] and has been successfully used for the synthesis of unsaturated lactones.[5] Thus, the combination of RCM and enantioselective reaction giving chiral diolefinic esters offers a new approach to chiral unsaturated lactones.

We have been involved in the asymmetric catalysis of planar-chiral cyclopentadienyl-ruthenium (Cp′Ru) complexes (**1**).[6,7] Recently, we reported the highly regio- and enantioselective allylic substitution of mono-substituted allylic chlorides with oxygen nucleophiles to give allylic ethers, esters, and alcohols in good yields.[8] As the resulting compounds are useful chiral building blocks because they have reactive terminal olefins, we focused our attention on the further transformation of allylic esters by RCM. We describe herein a new synthetic route to optically active lactones *via* asymmetric allylic carboxylation followed by RCM. Very recently, Feringa and coworkers reported a similar approach to optically active γ-lactones, which was based on Cu-catalyzed asymmetric allylic alkylation and RCM.[9] However, the reaction has some limitations because a Grignard reagent is used as an alkyl source in the asymmetric allylic substitution, and the formation of styrene as a byproduct of metathesis is unfavorable from the viewpoint of atom economy.

First, we investigated the asymmetric allylic carboxylation of cinnamyl chloride (**2a**) with α,β-unsaturated carboxylate.

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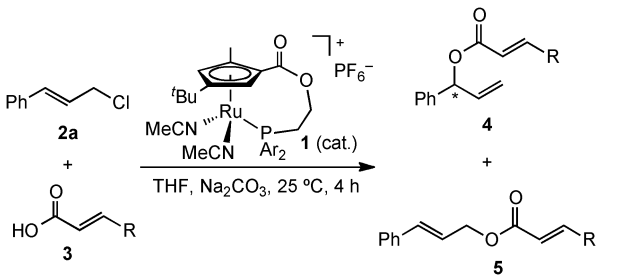
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data of new compounds. See DOI: 10.1039/c2cc18137a

Table 1 Screening of reaction conditions[a]



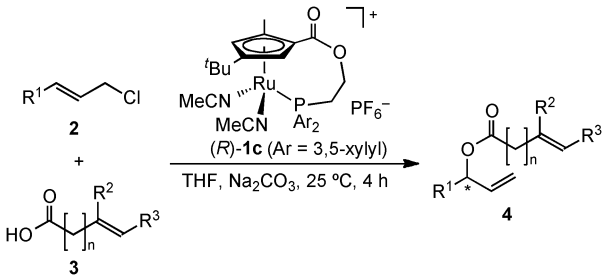
Entry	Catalyst	Carboxylic acid	**2a**/**3**	Yield[b] (%)	**4**/**5**[c]	ee[d] (%)
1	*rac*-**1a** (Ar = Ph)	**3a** (R = H)	2.0	61	1/1	—
2	*rac*-**1a**	**3a**	5.0	95	1/1	—
3	*rac*-**1a**	**3b** (R = Me)	2.0	98	>20/1	—
4	(*R*)-**1a**	**3b**	2.0	99	>20/1	88
5	(*R*)-**1b** (Ar = *o*-tolyl)	**3b**	2.0	82	1/1	54
6	(*R*)-**1c** (Ar = 3,5-xylyl)	**3b**	2.0	97	>20/1	97

[a] Reaction conditions: **3** (0.5 mmol), cat. (1 mol%), Na_2CO_3 (1.5 mmol), THF (2 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis using a chiral stationary phase.

The representative results are summarized in Table 1. Treatment of **2a** with acrylic acid (**3a**) in a 2 : 1 ratio using 1 mol% of racemic Cp′Ru catalyst **1a** under basic conditions gave a 1 : 1 mixture of branched and linear allylic esters (**4aa** and **5aa**) in 61% yield (entry 1). As we have evidence that the use of an excess amount of **2a** suppresses the formation of linear ester,[8b] we performed the reactions using 5 equiv. of **2a**. Unfortunately, no significant change was observed in the selectivity of **4aa** and **5aa** although the yield increased to 95% (entry 2). However, high selectivity for the branched ester was achieved in the reaction that used *trans*-2-butenoic acid (**3b**) instead of **3a**. Treatment of **2a** with **3b** selectively produced **4ab** in 98% yield (entry 3). When (*R*)-**1a** was used as catalyst, **4ab** was obtained in 99% yield with 88% ee (entry 4). Meanwhile, (*R*)-**1b** that has *o*-tolyl groups on the phosphine ligand led to decreases in yield as well as regio- and enantioselectivities (entry 5), whereas (*R*)-**1c** having 3,5-xylyl groups showed high enantioselectivity (97% ee) with good yield and regioselectivity (entry 6).[8c]

The reactions of a variety of allylic chlorides with unsaturated carboxylates were conducted under optimized conditions (Table 2). Not only aryl-substituted allylic chlorides but also

Table 2 Regio- and enantioselective allylic carboxylation with planar-chiral Cp′Ru catalyst[a]



Entry	Allylic chloride	Carboxylic acid	Product	Yield[b] (%)	ee[c] (%)
1	**2a** (R^1 = Ph)	**3b** (R^2 = H, R^3 = Me, n = 0)	**4ab**	97	97
2	**2b** (R^1 = *p*-C_6H_4Br)	**3b**	**4bb**	99	96
3	**2c** (R^1 = *p*-$C_6H_4CF_3$)	**3b**	**4cb**	99	98
4	**2d** (R^1 = 1-naphthyl)	**3b**	**4db**	99	96
5	**2e** (R^1 = *p*-$C_6H_4CO_2Me$)	**3b**	**4eb**	99	95
6	**2f** (R^1 = CH_2OBn)	**3b**	**4fb**	97	90
7[d]	**2a**	**3c** (R^2 = Me, R^3 = H, n = 0)	**4ac**	99	94
8[e]	**2a**	**3d** (R^2 = H, R^3 = Me, n = 1)	**4ad**	99	97
9[e]	**2a**	**3e** (R^2 = R^3 = H, n = 2)	**4ae**	91	95

[a] Reaction conditions: **2** (1.0 mmol), **3** (0.5 mmol), (*R*)-**1c** (5 μmol), Na_2CO_3 (1.5 mmol), THF (2 mL). [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase. [d] (*R*)-**1c** (15 μmol). [e] **2a** (2.5 mmol), (*R*)-**1c** (15 μmol).

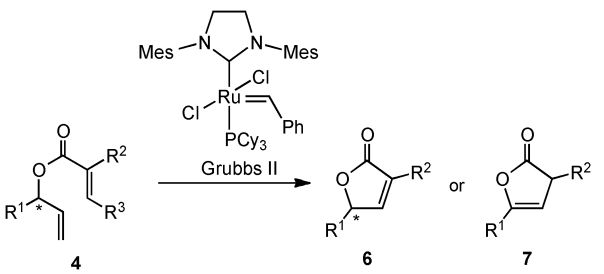
an alkyl-substituted one was applicable to the present system to give corresponding allylic *trans*-2-butenoates **4bb–4fb** in quantitative yields with excellent regio- and enantioselectivities (entries 2–6). The reaction with methacrylic acid (**3c**) produced allylic methacrylate **4ac** in 99% yield with 94% ee. Allylic esters **4ad** and **4ae** were obtained from the reactions with β,γ- and γ,δ-unsaturated carboxylates in good yields with high enantioselectivities, although 5 equiv. of **2a** was required for the high regioselectivity.

Then, the resulting allylic esters were subjected to RCM. As shown in Table 3, treatment of allylic esters with 2 mol% of the Grubbs II catalyst in CH_2Cl_2 resulted in the formation of corresponding α,β-unsaturated γ-lactones **6** in good yields (entries 1–4). High enantiomeric purities were achieved except for the reaction of 1-(*p*-carbomethoxyphenyl)allyl ester **4eb**. Simultaneous isomerization took place in the reaction of **4eb** to give achiral β,γ-unsaturated γ-lactones **7eb** in 75% yield (entry 5).

The reaction of β,γ-unsaturated ester **4ad** was tricky because parts of resulting β,γ-unsaturated δ-lactone **8** isomerized to α,β-unsaturated lactone **9**,[10] which could not be separated. After careful examination of the reaction conditions, we found that the reaction in CH_2Cl_2 at 30 °C for 12 h selectively produced **8** in 77% yield (Scheme 1). On the other hand, the addition of 2-propanol promoted the sequential isomerization to give **9** as the sole product in 56% yield.[11] Furthermore, the sequential treatment with hydrogen gave saturated δ-lactone **10** in 60% yield.[12] No loss of enantiopurity was observed in these tandem transformations.

When γ,δ-unsaturated ester **4ae** was treated under similar conditions, a complex mixture was obtained (Scheme 2). The formation of ε-lactone **11** could not be confirmed from the ^1H NMR spectrum. However, the ESI-MS spectrum exhibited a major peak due to the Na^+ adduct of dimer **12a** (n = 2) and a small peak due to the H^+ adduct of desired ε-lactone **11** was detected as well. As small peaks assignable

Table 3 RCM of allylic α,β-unsaturated carboxylates giving γ-lactones[a]

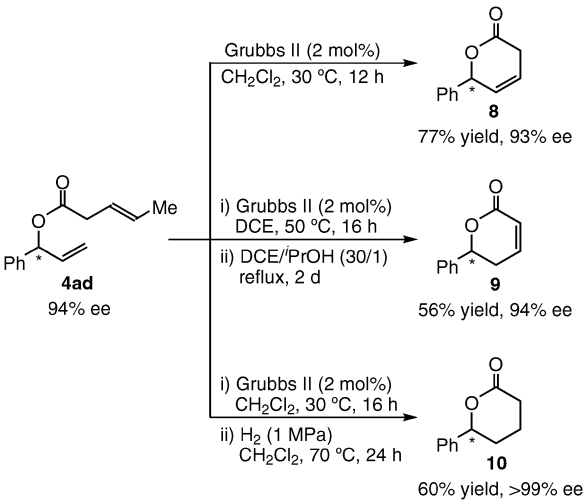


Entry	Ester	Product	Yield[b] (%)	ee[c] (%)
1	**4ab** (R^1 = Ph, R^2 = H, R^3 = Me, 97% ee)	**6ab**	89	97
2	**4bb** (R^1 = *p*-C_6H_4Br, R^2 = H, R^3 = Me, 96% ee)	**6bb**	99	98
3	**4cb** (R^1 = *p*-$C_6H_4CF_3$, R^2 = H, R^3 = Me, 98% ee)	**6cb**	78	95
4[d]	**4db** (R^1 = 1-naphthyl, R^2 = H, R^3 = Me, 96% ee)	**6db**	62	99
5[d]	**4eb** (R^1 = *p*-$C_6H_4CO_2Me$, R^2 = H, R^3 = Me, rac)	**7eb**	75	—
6[d]	**4fb** (R^1 = CH_2OBn, R^2 = H, R^3 = Me, 90% ee)	**6fb**	82	95
7[d]	**4ac** (R^1 = Ph, R^2 = Me, R^3 = H, 94% ee)	**6ac**	82	97

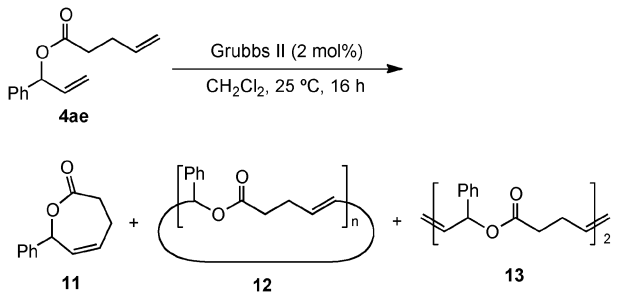
[a] Reaction conditions: **4** (0.3 mmol), Grubbs II (6 μmol), CH_2Cl_2 (6 mL), 25 °C, 16 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Reflux.

to the Na^+ adducts of trimer and tetramer **12b** and **12c** (n = 3 and 4) as well as linear dimer **13** were observed in the spectrum, **4ae** was suitable not for RCM but for the cross metathesis reaction.[13]

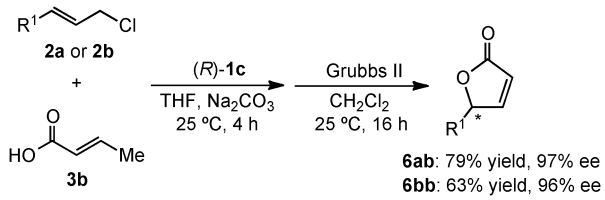
The efficient synthesis of optically active α,β-unsaturated γ-lactone **6** was achieved by one-pot sequential reactions, as shown in Scheme 3. The enantioselectivities of **6ab** and **6bb** were the same as those furnished by the two-step reactions,



Scheme 1 RCM of allylic β,γ-unsaturated carboxylates giving γ-lactones.



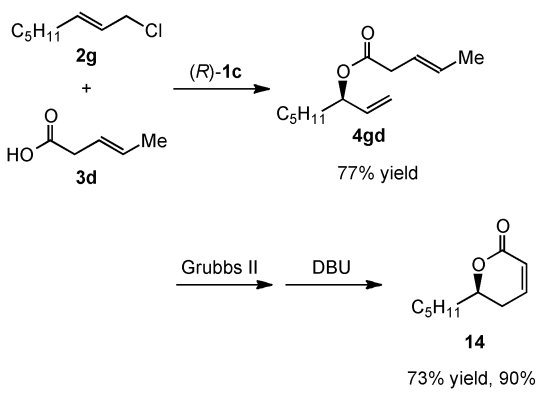
Scheme 2 Metathesis reaction of allylic γ,δ-unsaturated carboxylates.



Scheme 3 One-pot synthesis of γ-lactones.

although the yields were slightly lower (Tables 2 and 3, entries 1 and 2).

Finally, we examined the applicability of our method to the synthesis of a biologically active lactone (Scheme 4).[14] Treatment of 2-octenyl chloride (**2g**) with **3d** gave **4gd** in 77% yield though



Scheme 4 Enantioselective synthesis of (*R*)-massoialactone.

enantioselectivity was not determined at this stage. Unfortunately, the tandem RCM–isomerization by a Grubbs II catalyst was unsuccessful. However, the one-pot stepwise reactions of RCM and isomerization with DBU produced (*R*)-(–)-massoialactone **14** in 73% yield with 90% ee.[15] This protocol provides an easier route to **14** compared to the known ones.[16]

In conclusion, we have developed an efficient method for the synthesis of optically active unsaturated γ- and δ-lactones, which proceeds *via* asymmetric allylic carboxylation with planar-chiral Cp′Ru catalyst and RCM with Grubbs II catalyst. This protocol was successfully applied to the enantioselective synthesis of (*R*)-(−)-massoialactone. The broad scope of allylic chloride in the present reaction underscores its high potential for the synthesis of bioactive organic compounds with unsaturated γ- and δ-lactone skeletons.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (Japan) as well as the Sumitomo Foundation.

Notes and references

1 (*a*) I. Collins, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1377; (*b*) V. Boucard, G. Broustal and J. M. Campagne, *Eur. J. Org. Chem.*, 2007, 225.
2 (*a*) E. L. Carswell, M. L. Snapper and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2006, **45**, 7230; (*b*) B. M. Trost and J. Hitce, *J. Am. Chem. Soc.*, 2009, **131**, 4572.
3 (*a*) S. P. Brown, N. C. Goodwin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 1192; (*b*) H. Ube, N. Shimada and M. Terada, *Angew. Chem., Int. Ed.*, 2010, **49**, 1858.
4 S. Monfette and D. E. Fogg, *Chem. Rev.*, 2009, **109**, 3783.
5 A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199.
6 (*a*) N. Dodo, Y. Matsushima, M. Uno, K. Onitsuka and S. Takahashi, *J. Chem. Soc., Dalton Trans.*, 2000, 35; (*b*) Y. Matsushima, N. Komatsuzaki, Y. Ajioka, M. Yamamoto, H. Kikuchi, Y. Takata, N. Dodo, K. Onitsuka, M. Uno and S. Takahashi, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 527.
7 (*a*) Y. Matsushima, K. Onitsuka, T. Kondo, T. Mitsudo and S. Takahashi, *J. Am. Chem. Soc.*, 2001, **123**, 10405; (*b*) K. Onitsuka, Y. Matsushima and S. Takahashi, *Organometallics*, 2005, **24**, 6472.
8 (*a*) K. Onitsuka, H. Okuda and H. Sasai, *Angew. Chem., Int. Ed.*, 2008, **47**, 1454; (*b*) N. Kanbayashi and K. Onitsuka, *J. Am. Chem. Soc.*, 2010, **132**, 1206; (*c*) N. Kanbayashi and K. Onitsuka, *Angew. Chem., Int. Ed.*, 2011, **50**, 5197.
9 B. Mao, K. Geurts, M. Fananas-Mastral, A. W. van Zijl, S. P. Fletcher, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2011, **13**, 948.
10 A. E. Sutton, B. A. Seigal, D. F. Finnegan and M. L. Snapper, *J. Am. Chem. Soc.*, 2002, **124**, 13390.
11 B. Schmidt, *Chem. Commun.*, 2004, 742.
12 J. Louie, C. W. Bielawski and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 11312.
13 E. B. Pentzer, T. Gadzikwa and S. T. Nguyen, *Org. Lett.*, 2008, **10**, 5613.
14 C. Bressy, F. Bargiggia, M. Guyonnet, S. Arseniyadis and J. Cossy, *Synlett*, 2009, 565.
15 G. W. K. Cavill, D. V. Clark and F. B. Whitfield, *Aust. J. Chem.*, 1968, **21**, 2819.
16 (*a*) W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, 1980, **45**, 4117; (*b*) M. M. Midland, A. Tramontano, A. Kazubski, R. S. Graham, D. J. S. Tsai and D. B. Cardin, *Tetrahedron*, 1984, **40**, 1371; (*c*) F. Bennett, D. W. Knight and G. Fenton, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1543; (*d*) S. Takano, M. Setoh and K. Ogasawara, *Tetrahedron: Asymmetry*, 1992, **3**, 533; (*e*) P. V. Ramachandran, M. V. R. Reddy and H. C. Brown, *Tetrahedron Lett.*, 2000, **41**, 583; (*f*) F. Marion, F. R. Le, C. Courillon and M. Malacria, *Synlett*, 2001, 138; (*g*) L. Fournier, P. Kocienski and J.-M. Pons, *Tetrahedron*, 2004, **60**, 1659; (*h*) R. Touati, V. Ratovelomanana-Vidal, H. B. Ben and J.-P. Genêt, *Tetrahedron: Asymmetry*, 2007, **17**, 3400; (*i*) L. Carosi and D. G. Hall, *Can. J. Chem.*, 2009, **87**, 650; (*j*) J. M. Oliveira, J. C. R. Freitas, J. V. Comasseto and P. H. Menezes, *Tetrahedron*, 2011, **67**, 3003; (*k*) A. Harbindu and P. Kumar, *Synthesis*, 2011, 1954.

