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Efficient phthalate-tethered ring-closing metathesis as a cross-coupling reaction

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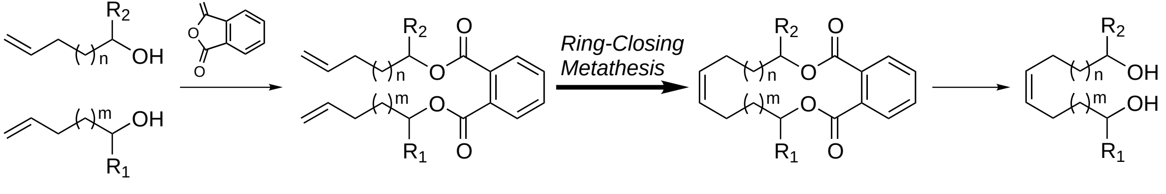
Abstract—An efficient method for cross-coupling using phthalate-tethered ring-closing metathesis was developed. Based on this method, the stereocontrolled syntheses of both (*R*,*R*)- and (*S*,*R*)-1-methoxypentadecane-2,9-diol (**17**, **20**) were achieved from (*R*)-1-undecen-5-ol (**4e**) and (*R*)-1-methoxy-5-hexen-2-ol (**13**). © 2001 Elsevier Science Ltd. All rights reserved.

Carbon–carbon bond formation is indispensable in organic synthesis. Particularly efficient cross-coupling reactions are required for the convergent syntheses of complex compounds. Recently, olefin metathesis, especially ring-closing metathesis, is often used for the synthesis of various compounds as an efficient reaction providing a C–C double bond under mild conditions.[1] Although cross-coupling reactions using olefin metathesis (cross metathesis) have been also reported,[2] these reactions essentially involve a concomitant competitive homo-coupling reaction.[3] We report here an alternative method for the cross-coupling of alkenes, employing ring-closing metathesis of the temporarily phthalate-tethered compounds[4,5] (Scheme 1).

Some tethered ring-closing metathesis approaches using 1,2-benzenedimethanol,[6] dichlorodiphenylsilane,[7] or dichlorodimethylsilane[8] as a linking reagent to connect two different alkenes have been reported.[9] In these cases, there is a possibility of formation of a by-product having two similar alkenes on the linker, which can afford a homo-coupling product in the ring-closing metathesis. To avoid this occurrence, we chose phthalic anhydride as a linking reagent.[4] Thus, reaction of a first alkenol with phthalic anhydride should exclusively give a half-ester, which could easily connect with a second alkenol to afford a phthalate linking two different alkenes.

First, the cross-coupling reactions of primary alcohols having a terminal olefin with a different methylene carbon chain were demonstrated (Scheme 2, Table 1, entry 1–3). Treatment of 4-pentenol (**1**) with phthalic anhydride (**2**) provided a half-ester **3** in 98% yield, which was esterified with allyl alcohol (**4a**), 3-butenol (**4b**), and 5-hexenol (**4c**) by DCC and DMAP to give diesters **5a**, **5b**, and **5c**, respectively, in high yield. Ring-closing metathesis reactions of **5a**–**c** were performed with Grubbs catalyst $RuCl_2(=CHPh)(PCy_3)_2$ **6** in CH_2Cl_2 at room temperature to afford the cyclized products **7a**–**c** having 12-, 13-, and 15-membered rings, respectively, in 85–99% yield as a mixture of *cis*- and *trans*-isomers. Next, the cross-coupling reactions of secondary alcohols were examined (Table 1, entries 4 and 5). Diesters **5d** and **5e** were prepared from the half-ester **3** with (*R*)-1-decen-4-ol (**4d**)[10] and (*R*)-1-undecen-5-ol (**4e**),[10] respectively, by the DCC/DMAP method. A



Scheme 1.

Keywords: metathesis; coupling reaction; stereocontrol; remote chiral centers.

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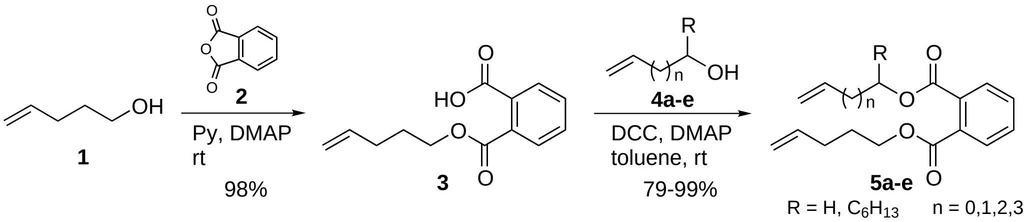
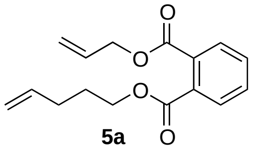
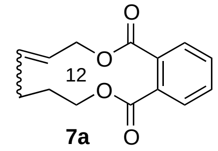
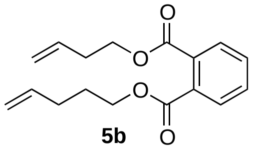
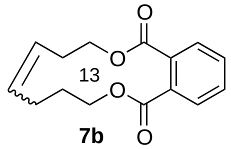
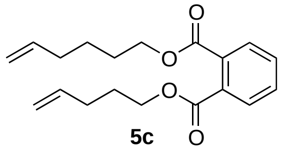
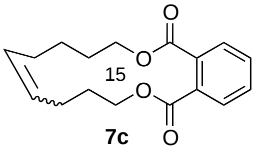
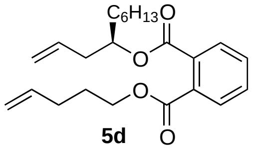
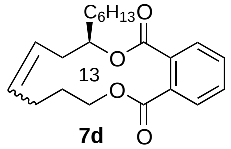
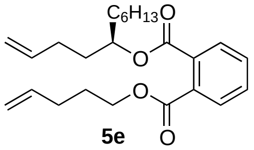
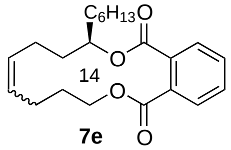
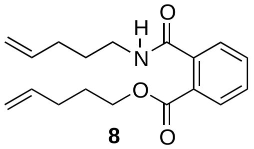
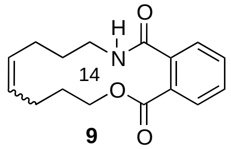


Scheme 2.

Table 1. Ring-closing metathesis reactions of phthalate-tethered dienes

Entry	Substrate	Products	Time[a] (h)	Yield (%)	*cis*/*trans* Ratio[b]
1	 **5a**	 **7a**	1.5	89	1.3 : 1
2[c]	 **5b**	 **7b**	1.75	99	1 : 1.7
3[c]	 **5c**	 **7c**	4.75	85	1.1 : 1
4	 **5d**	 **7d**	3.3	99	1 : 2.4
5	 **5e**	 **7e**	1.0	92	6.8 : 1
6	 **8**	 **9**	1.0	85	13 : 1

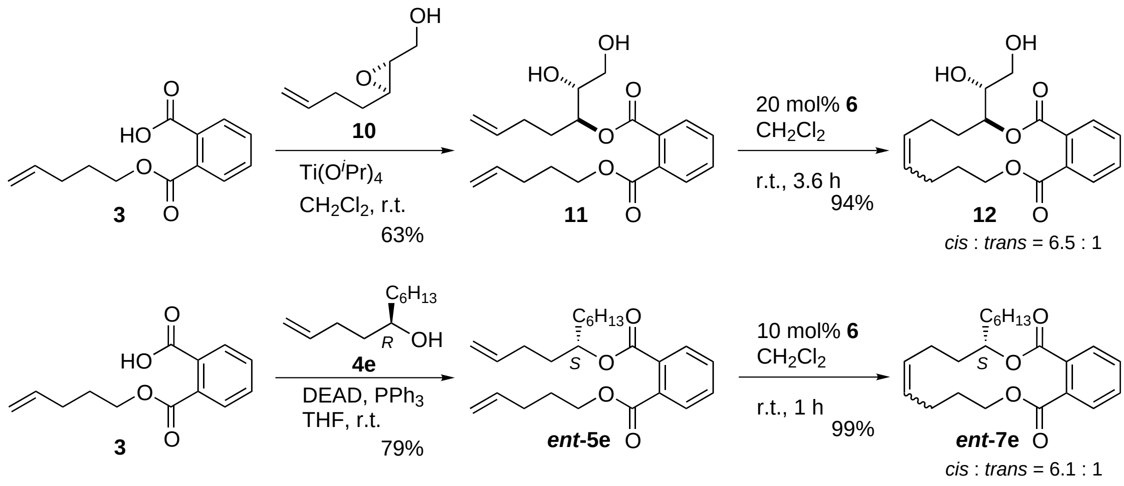
[a] All reactions were carried out with 2.5 mM of substrate and 10 mol% of **6** in CH_2Cl_2 at room temperature, unless otherwise noted.

[b] Determined by ^{1}H NMR spectroscopy.

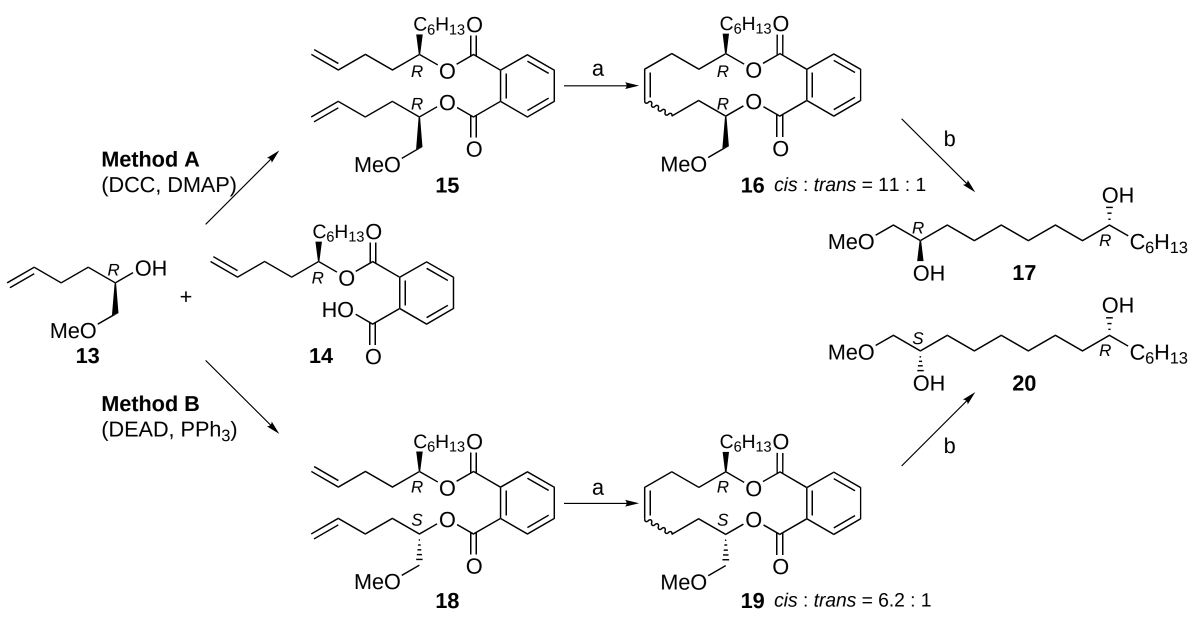
[c] Performed with 20 mol% of **6**.

cyclized product **7d** was obtained by treatment of **5d** with Ru catalyst **6** in almost the same yield and stereoselectivity as **7b**. Interestingly, ring-closing metathesis of **5e** provided a 14-membered product **7e** with modest *cis* selectivity. These results showed that the ring-closing metathesis of the phthalate-tethered dienes occurred in high yield and that the stereoselectivity would depend on the ring size.

An important characteristic of the phthalate-tethered ring-closing metathesis is the fact that the half-ester is a useful synthetic intermediate utilized in various reactions. For example, the half-ester **3** was able to give amide **8** by reaction with 4-pentenyl amine in the presence of EDC·HCl (Table 1, entry 6). Thus, the ring-closing metathesis of **8** affording **9** has enabled the cross-coupling between alkenol and alkenyl amine. The half-ester **3** can also be used as a nucleophile (Scheme 3). Reaction of **3** with epoxide **10**[11] using Ti(O*i*-Pr)$_4$ effected the regioselective epoxide-opening to give diol **11** with inversion.[12] Treatment of diol **11** with catalyst **6** gave a



Scheme 3.



Scheme 4. *Reagents and conditions*: (a) 10 mol% **6**, CH$_2$Cl$_2$, 1 h, 94% for **16**, 99% for **19**; (b) (i) NaOMe, MeOH, 40°C, (ii) H$_2$, Pd/C, EtOH, 82% for **17**, 86% for **20** in two steps.

cyclized diol **12** in 94% yield. It is important that the amide proton in **8** and the free hydroxyl group in **11** do not interfere in the present cross-coupling. The Mitsunobu reaction[13] of the half-ester **3** and (*R*)-1-undecen-5-ol (**4e**) by using DEAD and PPh$_3$ provided a diester ***ent*-5e**, the enantiomer of **5e**, which gave a macrocycle ***ent*-7e** by ring-closing metathesis. Thus, stereoisomeric cross-coupling products can be produced independently from the same segments by selection of the conditions in this cross-coupling.

Based on this concept, the diastereomers **17** and **20** having two remote chiral centers were synthesized by the present phthalate-tethered ring-closing metathesis (Scheme 4). Diesters **15** and **18** were prepared from (*R*)-1-methoxy-5-hexen-2-ol (**13**)[14] and a half-ester **14**[15] by the DCC/DMAP and DEAD/PPh$_3$ methods, respectively. The ring-closing metathesis of **15** and **18** followed by methanolysis and hydrogenation afforded (*R*,*R*)- and (*S*,*R*)-1-methoxypentadecane-2,9-diol (**17**, **20**), respectively, in good yield.

In summary, an efficient phthalate-tethered ring-closing metathesis as a cross-coupling reaction was developed and the stereocontrolled synthesis of the diastereomers having remote chiral centers was demonstrated. The present methodology could be applied to syntheses and stereochemical elucidations of natural products having undefined stereochemistry.

Acknowledgements

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10. **4d** and **4e** were prepared by addition of vinyl and allyl Grignard reagents, respectively, with CuI to (*R*)-1,2-epoxyoctane purchased from AZmax Co. Ltd.
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15. **14** was prepared from **4e** and phthalic anhydride.