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A highly enantioselective one-pot synthesis of homoallylic alcohols via tandem asymmetric allyl transfer/olefin cross metathesis

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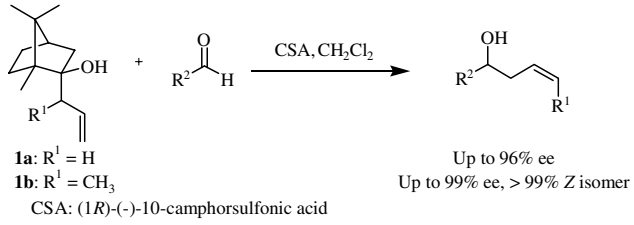
Abstract—A highly enantioselective one-pot synthesis of linear homoallylic alcohols with terminal ester functionality has been achieved. The reactions were controlled by ordered addition of reagents and catalysts, ensuring complete consumption of aldehyde. The synthetic utility of this strategy has been demonstrated in a short synthesis of a low boiling point intermediate for grahamimycin A.

Attainment of high efficiency is one of the fundamental objectives in chemical synthesis. Among various strategies, tandem reactions have attracted the most attention[1] due to their ability to shorten reaction times as well as reduce yield losses associated with extraction and purification of intermediates in multi-step sequences. Accordingly, considerable effort has been directed towards the development of new tandem reactions. Recently, asymmetric tandem reactions have gained increasing importance in many chemical transformations involving two steps or more, giving rise to highly functionalized compounds with high enantio- and/or regioselectivities.[2]

In our group, we have been interested in the development of new methods to obtain enantiomerically enriched linear homoallylic alcohols. The enantioselective allyl transfer to carbonyl compounds using camphor-derived homoallylic alcohols (**1a** and **1b**) can be effectively carried out to afford the corresponding homoallylic alcohols with excellent selectivities and good yields (Scheme 1).[3] However, one of the limitations of this rearrangement is the inability of this strategy to afford linear homoallylic alcohols where $R^1 = CO_2Et$.[4]

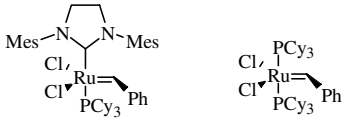


Scheme 1. Allyl transfer using (+)-camphor.

To circumvent this problem, we envisaged that a tandem reaction involving asymmetric allyl transfer followed by olefin cross metathesis (CM) would provide an easy access to a wide variety of linear enantiomerically enriched and geometrically defined homoallylic alcohols.

Over the past decade, the Ru complexes **2** and **3** have been extensively used in olefin metathesis (Fig. 1).[5]

While the intramolecular metathesis reactions have been found to be a powerful method especially for the



2 **3**

Figure 1. Ruthenium-based complexes.

Keywords: Homoallylic alcohols; Allyl transfer; Tandem reactions; Olefin cross metathesis.
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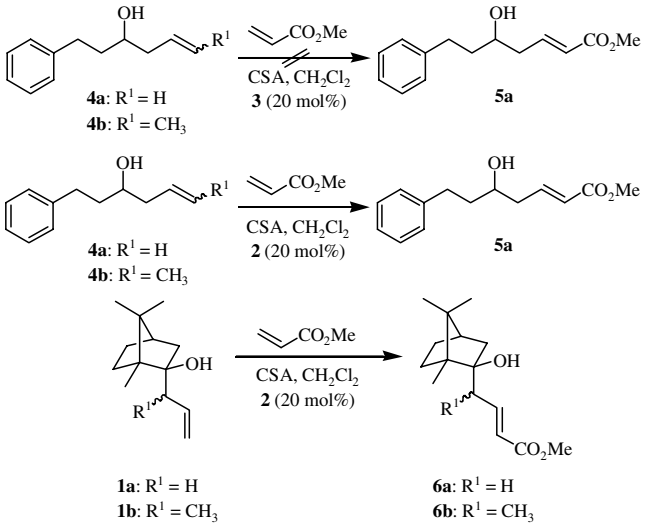
construction of cyclic molecules, intermolecular versions of this important reaction have gained increasing importance where the scope and limitations have been systematically studied by numerous researchers.[6] Herein, we report a one-pot tandem reaction involving asymmetric allyl transfer and olefin cross metathesis.

To check the feasibility of the olefin cross metathesis under the asymmetric allyl transfer conditions, a few control reactions were carried out. First, homoallylic alcohols **4a** and **4b** were subjected to Grubbs' catalysts[5] (Scheme 2). Catalyst **3** did not catalyze the cross metathesis reaction. It is worth noting that the reaction with homoallylic alcohols **4a** and **4b** proceeded in moderate yields of 67% ($R^1 = H$) and 62% ($R^1 = CH_3$) in the presence of CSA without protection of the hydroxyl group.

Next, we investigated the cross metathesis using both camphor-derived homoallylic alcohols (**1a** and **1b**) and methyl acrylate (Scheme 2). The reaction involving **1a** afforded the CM product in 51% yield. On the other hand, the reaction involving **1b** afforded the product in much lower yield (<5%). This result is consistent with the recent studies by Grubbs[6c] who demonstrated that branched olefin substrates perform less well in cross metathesis as compared to linear substrates. Hence, **1b** was employed for the tandem reaction as a lesser amount of undesired by-product was observed.

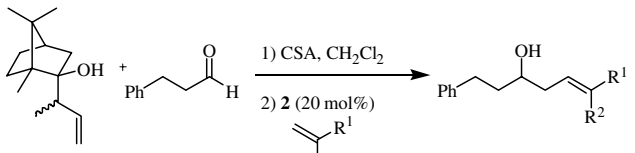
Based on the above results, we carried out the one-pot tandem allyl transfer and olefin cross metathesis reaction using hydrocinnamaldehyde **7a** and methyl acrylate (Table 1, entry 1). A good yield of 54% and an excellent ee of 94% were obtained.

Next, we explored a few other olefinic compounds (Table 1, entries 2–4). Generally, the enantioselectivities were comparable for all entries. No product was observed when methyl methacrylate was employed (Table 1, entry 3). We believe that one of the reasons for this is the inability of branched olefins to undergo olefin cross metathesis. However, the tandem product was observed from a reaction involving methacrolein (Table 1, entry 4), with the lower yield obtained, being mainly due to the decrease in the reactivity of branched olefins towards cross metathesis as mentioned earlier.

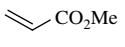
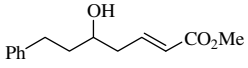
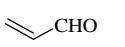
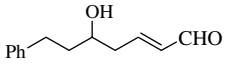
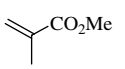
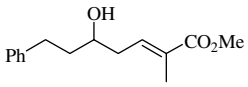
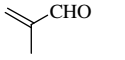
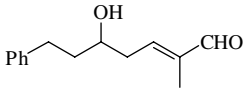


Scheme 2. Various olefin cross metathesis reactions.

Table 1. Tandem reactions using different olefinic compounds



1b *syn/anti* = 70:30 **7a** **5**

Entry	Olefinic compound	Product	Yield (%)[a]	% ee[b]
1			54	94
2			46	94
3			0	—
4[c]			30	94

[a] Isolated yield.
[b] Determined by HPLC analysis using Chiralcel columns or ^{1}H NMR analysis of the Mosher acid derivatives. Please refer to the supporting information.
[c] Double bond geometry determined using ^{1}H and ^{13}C NMR.

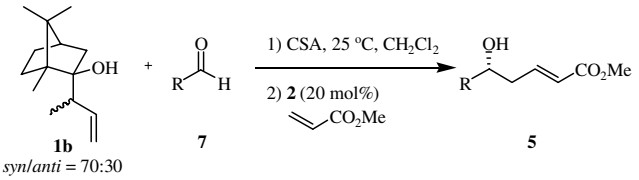
With the success obtained using methyl acrylate for cross metathesis in the tandem reaction, we carried out the tandem reaction using methyl acrylate with various aldehydes, as shown in Table 2.

Generally, only the *E* isomer was observed[7] in all cases (>99%). Notably, the olefin cross metathesis step tolerates the α,β-unsaturated functionality, affording the cross metathesis product in a moderate yield of 46% and an excellent ee of 96% (Table 2, entry 3).

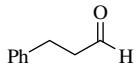
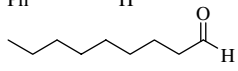
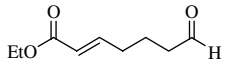
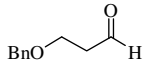
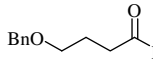
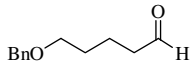
The synthetic value of this protocol is demonstrated in the preparation of homoallylic alcohol **8**, which is an important precursor in the synthesis of grahamimycin A (Scheme 3). This macrocyclic dilactone exhibits excellent antibacterial and antifungal activities towards pathogenic microorganisms.[8] Homoallylic alcohol **8** was previously synthesized via a synthetic route involving allylation, ozonolysis and Wittig reactions.[9] Employing our tandem methodology as demonstrated above, the low boiling point precursor **8** was obtained in a moderate yield of 62% with an excellent enantioselectivity of 92% (Scheme 3). In this case, (−)-camphor-derived homoallylic alcohol **1c** was employed in order to obtain the desired enantiomer responsible for the biological activity.

In conclusion, we have successfully demonstrated a highly efficient one-pot tandem asymmetric allyl transfer

Table 2. Tandem asymmetric allyl transfer and olefin CM with various aldehydes

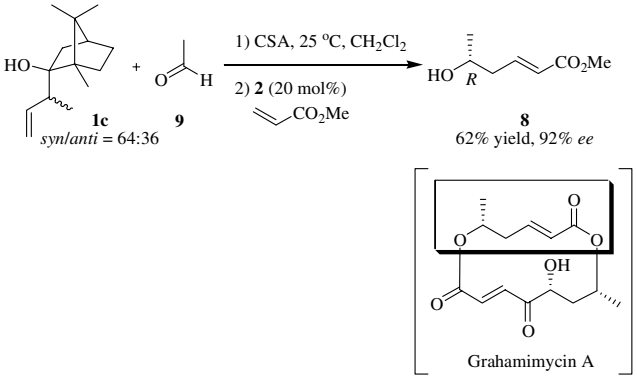


1b *syn/anti* = 70:30 **7** **5**

Entry	RCHO	Time (h)	Yield (%)[a]	% ee[b]
1		122	54	94
2		126	58	94
3		126	46	96
4		127	46	96
5		150	52	94
6		126	50	94

[a] Isolated yield.

[b] Determined by HPLC analysis using Chiralcel columns or ^{1}H NMR analysis of the Mosher acid derivatives. Please refer to the supporting information.



Scheme 3. Synthesis of homoallylic alcohol **8**.

and cross olefin metathesis reaction,[10] producing linear homoallylic alcohols in good yields and excellent enantioselectivities. In all cases, the reactions are controlled by the ordered additions of reagents and catalysts, thus making it a versatile approach for many synthetic reactions. In this one-pot reaction, no protection of the hydroxyl group is required and selective cross-coupling metathesis is achieved (Table 2, entry 3). The procedure made use of the more reactive product as compared to starting materials (<5% undesired by-product observed). Furthermore, the protocol can be applied to low boiling point compounds as demonstrated in the short synthesis of alcohol **8**,[11] a key intermediate in the synthesis of grahamimycin A.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.078.

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7. Only the *E* isomer was obtained as observed from ^{1}H NMR data.
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10. General experimental procedure for the tandem reaction yielding **5a**: to a solution of (1*R*)-(−)-10-camphorsulfonic acid (CSA) (7 mg, 0.03 mmol, 0.1 equiv) and hydrocinnamaldehyde **7a** (47 mg, 0.3 mmol, 1.0 equiv) in dichloromethane (0.1 mL, 3 M) under nitrogen at 25 °C was added **1b** (187 mg, 0.9 mmol, 3.0 equiv). The reaction mixture was allowed to stir for 5–6 days. Upon complete consumption of **7a**, the reaction mixture was diluted with 0.5 mL dichloromethane (0.5 M) and methyl acrylate (81 μL, 0.9 mmol, 3.0 equiv) was added, followed by Grubbs' second generation catalyst (127 mg, 0.015 mmol, 0.05 equiv). Sequential addition of Grubbs' catalyst (127 mg, 0.015 mmol, 0.05 equiv) was carried out thrice at 30 min time intervals, and the reaction mixture was allowed to stir for another 2 h. Upon completion, the reaction was filtered through filter agent through Celite® 521 packed in a sintered glass funnel (∼20 mm depth) and the filtrate concentrated in vacuo. The crude product was purified via silica gel chromatography using hexane–ethyl acetate (25:1) as eluent to afford the product **5a** as a faint yellow oil (38 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.16 (m, 5H), 6.97 (ddd, $J = 15.7$, 8.0, 7.7 Hz, 1H), 5.90 (dt, $J = 15.7$, 1.4 Hz, 1H), 3.84–3.76 (br m, 1H), 3.72 (s, 3H), 2.85–2.63 (m, 2H), 2.40 (t, $J = 7.0$ Hz, 2H), 1.84–1.77 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.7, 145.1, 141.6, 128.5, 128.4, 126.0, 123.7, 69.9, 51.5, 40.3, 38.7, 32.0; FTIR (neat, NaCl): 3434, 3027, 2945, 2851, 1721, 1655, 1437, 1325, 1276, 1174, 1045, 980, 748, 701 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}O_3$ [M^+]: 234.1256. Found: 234.1256; $[\alpha]_D$ −10.8 (*c* 1.0, CH_2Cl_2).
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