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Enantioselective synthesis of bicyclic compounds via catalytic 1,4-addition-ring closing metathesis†

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A novel three step asymmetric annulation procedure comprises a tandem catalytic enantioselective 1,4-additionallyc substitution, Grignard addition and ring closing metathesis (RCM) sequence to provide [6,6], [7,6], [8,6] and [6,7] bicyclic products with ee’s of 93–97% in which the size of both rings can easily be varied independent of each other.

Novel routes to carbocyclic compounds in enantioselectively pure form continue to offer a synthetic challenge since numerous products including terpenes and steroids show this structural feature. A classical example is found in the synthesis of (±)-d-homo-19-nortestosterone starting from the readily available Wieland–Miescher ketone for which an asymmetric synthesis proceeds via the Hajos–Parrish version of the Robinson annulation.¹ ² In the pursuit of novel catalytic asymmetric annulation strategies we focus on the construction of enantioselectively pure carbocyclic products with various ring sizes.³

Since the pioneering work by the groups of Grubbs and Schrock, ring closing metathesis (RCM) has become a powerful tool for the synthesis of a variety of cyclic structures.⁴ Especially for medium sized and macrocyclic ring systems, which are difficult or even impossible to make by other methods, RCM proved to be highly valuable.⁵ As a result of the remarkable tolerance of the Grubbs catalyst towards various functional groups, RCM is increasingly applied in novel product synthesis.⁶

We envisioned that by making use of a combination of RCM and the copper–phosphoramidite based catalytic enantioselective 1,4-addition developed in our laboratories, a variety of enantioselectively pure bicyclic products would become readily accessible. In these bicyclic products both ring sizes can easily be varied, independent of each other. The following considerations were made: (i) cyclic enones with different ring sizes and substituents can be employed in the catalytic 1,4-addition with enantioselectivities generally exceeding 96% in the products. These products can subsequently act as templates onto which a second ring can be annulated.⁷ (ii) The use of RCM for this annulation would make different ring sizes in the second ring accessible. In these bicyclic products both ring sizes can easily be varied independent of each other. The following considerations were made: (i) cyclic enones with different ring sizes and substituents can be employed in the catalytic 1,4-addition with enantioselectivities generally exceeding 96% in the products. These products can subsequently act as templates onto which a second ring can be annulated.⁷ (ii) The use of RCM for this annulation would make different ring sizes in the second ring accessible.⁸

To examine the viability of this approach we synthesized 2-allyl-3-alkylcycloalkanones 2a–f by a tandem 1,4-additionallyc substitution reaction.⁹ ¹⁰

As is shown in Scheme 1 the zinc enolate resulting from the catalytic 1,4-addition of dialkylzinc reagent to cycloalkenones in the presence of phosphoramidite ligand (S,R,R)-3 (1 mol%) and Cu(OTf)₂ (0.5 mol%) was trapped stereo- and regioselectively by the Pd–allyl complex in situ generated from allyl acetate and a catalytic amount of Pd(PPh₃)₄, giving dissubstituted cycloalkanones 2a–f in good yields and with ee’s ranging from 93 to 97% (Table 1). Furthermore a trans–cis ratio of 9 : 1 or higher is observed in all cases except for 2e (entry 5).¹⁰ In the case of 2b and 2d complete diastereoselectivity towards the trans isomer is found.

By introducing a second terminal alkene moiety via the 1,2-addition of suitable Grignard reagents such as vinyl-, allyl- and butenylmagnesium halides to 2a–f, the corresponding dienes 4a–h are formed which are next converted to carbocyclic structures 6a–h by RCM as is shown in Scheme 2. Table 2 summarizes the results of this new enantioselective method for the preparation of carbocyclic structures. As expected, a reasonable selectivity was observed for the addition

† Electronic supplementary information (ESI) available: NMR spectra and detailed explanation. See http://www.rsc.org/suppdata/cc/b1/b100283j/

Table 1 Tandem-1,4-addition-allylic substitution to cyclic enones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>n</th>
<th>R¹</th>
<th>R</th>
<th>C.y. 2 (%)a</th>
<th>ee 2 (%)b</th>
<th>trans–cis</th>
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<tr>
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<td>1a</td>
<td>1</td>
<td>H</td>
<td>Et</td>
<td>2a</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2</td>
<td>H</td>
<td>Et</td>
<td>2b</td>
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<td>1d</td>
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<td>Me</td>
<td>Et</td>
<td>2d</td>
<td>82</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>2e</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>1</td>
<td>H</td>
<td>Bu</td>
<td>2f</td>
<td>83</td>
<td>93</td>
</tr>
</tbody>
</table>

a Isolated yield after column chromatography. b Determined by chiral GC (ChiralDEX G-TA). c Determined by GC. d Not determined. e Only trans detected.

Scheme 1

Scheme 2

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of the Grignard reagents to 2a–f in all cases and the major isomer results from the attack of the Grignard reagent trans to the allyl group leading to the all-trans isomer as the major product (Scheme 2). Addition of allylmagnesium chloride (m = 1, entry 1) to a 90:10 trans–cis mixture of 2a yields three out of four possible diastereomers of 4a in a ratio of 74:16:10 as judged by GC. This result is explained as follows: addition of the Grignard reagent to the trans compound (2R,3S)-2a proceeds preferably trans to the allyl group but not with complete selectivity accounting for 74% (1R,2R,3S)-1,2-diallyl-3-ethylcyclohexanol (4a) and 16% (1S,2R,3S)-4a. The relative configuration of the major isomer was determined by COSY, HSQC and NOESY NMR experiments on the p-nitrobenzoate ester of 6a.† Addition to the minor cis compound (2S,3S)-2a accounts for the 10% of another isomer of 4a, most probably (1S,2S,3S)-4a. In the case of trans-2b the ratio of trans and cis addition is 80:20 and pure trans-4b (68%) could be isolated by column chromatography. The addition to trans-2c proceeds with a moderate selectivity giving a trans/cis ratio of 63:37. Addition of butenylmagnesium bromide (m = 2) to a 9:1 trans–cis mixture of 2a in THF at 0 °C required transmetallation to the organocerium reagent to prevent enolization and to give complete conversion to 4h as a mixture of 3 isomers (87:12:1) with (1R,2R,3S)-4h as the major product (entry 8). All dienes 4a–h readily undergo ring closure in benzene in the presence of 7.5 mol% of Grubbs catalyst 5, except for 4g. In the latter case formation of only a small amount of 6g was observed (entry 7). GC analysis revealed that only the cis isomer of 4g had been converted. The trans-fused 5,6-ring system is not formed, most probably due to the strain in such a system.12 Formation of a six membered ring (entries 1–6) proceeded well in all cases as 100% conversion was observed, indicating that both cis- and trans-fused ring systems are readily formed. Isomerically pure trans-diene 4d provided the 76-bicyclic product in 100% isolated yield. In all other cases the major isomer of the resulting carbocyclic products from this annulation protocol was isolated in moderate to good yield by simple chromatographic procedures with ee’s ranging from 93 to 97%. For example, (1S,9R,9aR)-6a could be isolated in 60% yield. Annulation of a seven membered ring by RCM was also successful as (15aR,9aR)-6h with an ee of 96% was isolated in 65% yield (entry 8).

In conclusion, new methodology for the synthesis of enantioselectively pure carbocyclic compounds has been developed, based on an enantioselective tandem 1,4-addition–allylic substitution, Grignard addition and RCM three step sequence. In contrast to most methodologies for asymmetric annihilations, which are restricted to specific ring sizes, the method presented here gives high enantioselectivities for the construction of a variety of bicyclic products. Products with[6,6], [7,6], [8,6] and [6,7] carbocyclic skeletons and different alkyl substituents have been prepared with ee’s ranging from 93–97%.

This work was supported by the Dutch Foundation for Scientific Research (NWO).

Notes and references

10 The relative configuration of the major isomer of 2a has previously been determined: M. Kitamura, T. Miki, K. Nakano and R. Noyori, Bull. Chem. Soc. Jpn., 2000, 73, 999.

Table 2 Grignard addition and RCM

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R1</th>
<th>n</th>
<th>m</th>
<th>C.y. 4 (%)</th>
<th>ee 4 (%)</th>
<th>Ring system</th>
<th>C.y. 6 (%)</th>
<th>ee 6 (%)</th>
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</thead>
<tbody>
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<td>H</td>
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<td>1</td>
<td>4a 92</td>
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</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>Et</td>
<td>H</td>
<td>1</td>
<td>2</td>
<td>4b 68†</td>
<td>96</td>
<td>6b [7,6]</td>
<td>100 96</td>
</tr>
<tr>
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<td>97</td>
<td>6c [8,6]</td>
<td>43 97</td>
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<tr>
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<td>2d</td>
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<td>1</td>
<td>4d 70</td>
<td>—</td>
<td>6d [6,6]</td>
<td>79 97</td>
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<tr>
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<td>1</td>
<td>4e 82</td>
<td>—</td>
<td>6e [6,6]</td>
<td>46 96</td>
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<td>1</td>
<td>4f 92</td>
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<td>6f [6,6]</td>
<td>46 96</td>
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<td>7</td>
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<td>Et</td>
<td>H</td>
<td>1</td>
<td>0</td>
<td>4g 64</td>
<td>—</td>
<td>6g [6,5]</td>
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<td>H</td>
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<td>2</td>
<td>4h 98</td>
<td>—</td>
<td>6h [6,7]</td>
<td>65 96</td>
</tr>
</tbody>
</table>

† Determined by chiral GC (Chiralpak G-TA). ‡ Not determined. § Isolated yield of all-trans isomer after column chromatography. * Determined by chiral HPLC after conversion into the p-nitrobenzoate ester. / Only a small amount (< 10%) of cis-fused 6g was detected by GC.