Diene hydroaminomethylation via ruthenium-catalyzed C–C bond forming transfer hydrogenation: beyond carbonylation†

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Under the conditions of ruthenium-catalyzed transfer hydrogenation using 2-propanol as terminal reductant, 1,3-dienes engage in reductive C–C coupling with formaldimines obtained in situ from 1,3,5-tris(aryl)-hexahydro-1,3,5-triazines to form homoallylic amines. Deuterium labelling studies corroborate a mechanism involving reversible diene hydoruthenation to form an allyl/ruthenium complex that engages in turn-over limiting imine addition. Protonolysis of the resulting amidoruthenium species releases product and delivers a ruthenium alkoxide, which upon β-hydride elimination closes the catalytic cycle. These transformations, which include enantioselective variants, represent the first examples of diene hydroaminomethylation.

Introduction

Rhodium catalyzed hydroformylation-reductive amination or “hydroaminomethylation” of α-olefins (Scheme 1, eqn (1)) has emerged as an important method for the synthesis of N-containing compounds, including pharmaceutical ingredients (e.g. cinacalcet, itubilide, and fexofenadine). Following its discovery at BASF in 1949 by Reppe, hydroaminomethylation initially received only a modest level of attention from academic and industrial researchers. The systematic studies of Eilbracht in the late 1990’s brought rhodium catalyzed hydroaminomethylation to the forefront of research, and in the last 15 years significant progress in this area was made. Notable achievements include the design of catalytic systems enabling direct use of ammonia, the ability to control regioselectivity in reactions of terminal alkenes as well as internal alkenes via ligand control or use of directing groups, and the development of the first ruthenium catalyzed carbonylative hydroaminomethylations.

Despite these advances, existing catalysts for hydroaminomethylation via hydroformylation-reductive amination are restricted to the use of nonconjugated alkenes, typically α-olefins. The carbonylative hydroaminomethylation of other π-unsaturated reactants, such as 1,3-dienes, has not been reported, as regioselectivity and “over-hydroformylation” to form dialdehydes are difficult to control (Scheme 1, eqn (2)). In connection with our exploration of hydrogenation and transfer hydrogenation in the context of reductive C–C coupling, we have found that paraformaldehyde serves as a convenient and inexpensive C1-building block for the hydrohydroxymethylation of 1,3-dienes, allenes, and alkynes. Most importantly, reductive couplings of paraformaldehyde provide access to products of hydrohydroxymethylation that cannot be formed selectively under hydroformylation conditions.

These results supported the feasibility of corresponding hydroaminomethylystions wherein π-unsaturated reactants are reductively coupled with formaldimines. In proof-of-concept studies, it was found that 1,1-disubstituted allenes engage in regioselective reductive coupling with formaldimines derived in situ through cracking of 1,3,5-tris(aryl)-hexahydro-1,3,5-
triazines under the conditions of ruthenium catalyzed transfer hydrogenation employing 2-propanol as terminal reductant. 

Corresponding hydroaminomethylations of 1,3-dienes such as butadiene, isoprene and myrcene, which are important feedstock chemicals, would be even more desirable, however, competingaza-Diels–Alder cycladdition and alkene isomerization of the homoallylic amines products rendered the outcome of such processes uncertain. Here, we report that ruthenium complexes modified by dCypm (bis(dicyclohexylphosphino)methane) catalyze the 2-propanol mediated reductive coupling of 2-substituted 1,3-dienes with 1,3,5-tris(aryl)-hexahydro-1,3,5-triazines to form products of hydroaminomethylation as single regioisomers with complete suppression of olefin isomerization in all but one case (Scheme 1, eqn (3)). These transformations represent the first examples of diene hydroaminomethylation.

Results and discussion

Hexahydro-1,3,5-triazine 2a is a white, crystalline solid conveniently prepared through the condensation of para-formaldehyde and para-anisidine. In an initial experiment, butadiene 1a was exposed to hexahydro-1,3,5-triazine 2a in the presence of 2-propanol (400 mol%) and commercial HClRu(CO)(PPh3)3 (5 mol%) in toluene solvent (0.5 M) at 120 °C. The targeted product of hydroaminomethylation 3a was obtained as a single isomer in 11% yield (Table 1, entry 1). A series of phosphine ligands were evaluated for their ability to enhance conversion. The isolated yield of 3a was not improved upon use of the monodentate phosphine ligands, for example PCy3 (Table 1, entry 2). A series of chelating bis(diphenylphosphino)-substituted ligands were screened, including dpdp, dpdm and dppe (Table 1, entries 3–5). The isolated yield of 3a was increased to 81% using dppe, however, substantial quantities of olefin isomerization product, allylic amine iso-3a, was formed (Table 1, entry 5). The chelating ligands dCypm and dCype, which incorporate bis(dicyclohexylphosphino) moieties, provided superior results, delivering the homoallylic amine 3a in 86% (10 : 1, 3a : iso-3a) and 71% (20 : 1, 3a : iso-3a) isolated yields, respectively (Table 1, entries 6 and 7). Attempts to enhance the performance of the dCypm-modified catalyst through variation of reaction temperature (Table 1, entries 8 and 9) or reaction time (Table 1, entry 10) did not add additional improvement (Table 2).

An attempt was made to apply these optimal conditions (Table, entry 6) to a series of 2-substituted 1,3-dienes 1b–1i, however, at 120 °C the desired products 3b–3i were accompanied by significant quantities of the corresponding aza-Diels–Alder [4 + 2] cycloadducts. 2-Substituted dienes display an enhanced conformational preference for the s-cis conformer, which increases their rate of Diels–Alder cycloaddition relative to butadiene. At slightly higher temperatures (140 °C in xylene solvent), competing Diels–Alder reaction decelerates with respect to hydroaminomethylation and could be completely suppressed. Using these slightly modified conditions, 2-substituted 1,3-dienes 1b–1i were reacted with hexahydro-1,3,5-triazine 2a to furnish the products of hydroaminomethylation 3b–3i in good yield as single regioisomers, and isomeric allylic amines iso-3b–3i were not observed. Notably, a range of substituents are tolerated at the 2-position of the diene, including branched aliphatic moieties (1d, 1f), groups with allylic heteroatoms (1d, 1e) and aryl groups (1g–1i). Under the present conditions, 1-substituted dienes engage in reductive coupling, however, lower conversions and selectivities were observed. To illustrate the utility of homoallylic amines 3a–3i, the hydroaminomethylation product 3b was transformed into the trisubstituted piperidine 4b via Prins reaction with glyoxylic acid mono-hydrate (Scheme 2, eqn (1))

Additionally, adduct 3i was subjected to N-allylation and ring closing metathesis to form the dissubstituted piperidine 4i (Scheme 2, eqn (2)).

Variation of the 1,3,5-tris(aryl)-hexahydro-1,3,5-triazine was subsequently investigated in the hydroaminomethylation of butadiene 1a (Table 3). N-Aryl substituted triazines 2a–2f were subjected to optimal conditions identified for the hydroaminomethylation of butadiene using triazine 2a (Table 1, entry 6). Electron rich N-aryl triazines 2a–2c, including ortho-substituted triazine 2c, undergo hydroaminomethylation efficiently to afford the branched homoallylic amines 3a–5a with complete regiocontrol. In each case, small quantities of the allylic amines iso-3a–5a were observed as side-products. Electron neutral triazine 2d and electron deficient triazines 2e and 2f were converted to the respective homoallylic amines 6a, 7a and 8a in good yield, although increased quantities of the allylic amine side-products were observed. As illustrated in the formation of 8a, nitrogen bearing heterocycles are tolerated. Attempted use of N-alkyl, N-acyl and N-sulfonyl triazines failed.
in the coupling with dienes under these initially developed conditions. It should be noted that the 3a–8a : iso-3a–8a ratio does not change as a function of conversion or reaction time, suggesting olefin isomerization is kinetically controlled, perhaps occurring by way of the homoallylic amidoruthenium intermediate (vida supra).

Having established favourable conditions for diene hydroaminomethylation, enantioselective variants were investigated in reactions of butadiene 1a. A survey of triazines 2a–2f revealed that triazine 2c derived from ortho-anisidine provided the highest levels of enantiomeric enrichment. Among various chiral phosphine ligands, (R)-MeO-furyl-BIPHEP provided the highest levels of enantiocontrol. In the presence of this chiral ligand, the reaction of 1,3-butadiene 1a with N-ortho-methoxyphenyl triazine 2c delivered the homoallylic amine 5a in 49% yield as a 94 : 6 ratio of enantiomers in the absence of allylic amine side-product iso-5a (Scheme 3). Application of these initially developed conditions for enantioselective hydroaminomethylation to isoprene resulted in the formation of homoallylic amine 5b in 54% yield as a 93 : 7 ratio of enantiomers.

### Table 2: Ruthenium catalyzed hydroaminomethylation of 1,3-dienes 1a–1i to form homoallylic amines 3a–3i via 2-propanol mediated transfer hydrogenation

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,3-Diene</th>
<th>Product</th>
<th>Yield (3 : iso-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1a</td>
<td>3a</td>
<td>86% yield</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>3b</td>
<td>79% yield</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>3c</td>
<td>76% yield</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>3d</td>
<td>71% yield</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>3e</td>
<td>74% yield</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>3f</td>
<td>70% yield</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>3g</td>
<td>77% yield</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>3h</td>
<td>72% yield</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>3i</td>
<td>81% yield</td>
</tr>
</tbody>
</table>

* Yields are of material isolated by silica gel chromatography. Isomeric ratios were determined via 1H NMR analysis. See ESI† for further experimental details.

### Table 3: Ruthenium catalyzed hydroaminomethylation of butadiene 1a with 1,3,5-tris(aryl)-hexahydro-1,3,5-triazines 2a–2f to form homoallylic amines 3a–8a

* Yields are of material isolated by silica gel chromatography. Isomeric ratios were determined via 1H NMR analysis. See ESI† for further experimental details.
enantiomers (Scheme 3). The absolute stereochemical assignment of 5a was determined by single crystal X-ray diffraction analysis of the corresponding 4-nitrobenzenesulfonamide.

Mechanistic studies

To illuminate key features of the catalytic mechanism, deuterium labelling studies of the ruthenium catalyzed hydroaminomethylation of isoprene 1b were performed (Scheme 4). Hydroaminomethylation of isoprene 1b using the deuterated triazine deuterio-2a provided deuterio-3b with complete retention of deuterium at the methylene carbon bearing nitrogen (>95% D). Deuterium was not detected at any other position. This experiment suggests deuterio-3b is inert with respect to amine dehydrogenation under these conditions. In a second experiment, isoprene 1b was subjected to hydroaminomethylation using triazine 2a in the presence of d8-2-propanol. As anticipated, the product deuterio-3b incorporates significant quantities of deuterium at the methyl group (65% D). However, deuterium also is incorporated at the terminal vinyl position (21% D) and, to a lesser extent, the allylic position (10% D). These data corroborate a scenario wherein rapid, reversible and non-regioselective diene hydrometalation occurs in advance of turn-over limiting imine addition. Reversible hydrometalation accounts for incomplete deuterium incorporation. Adventitious water also may diminish the extent of deuterium incorporation.25

Guided by these data, a mechanism for ruthenium catalyzed diene hydroaminomethylation via transfer hydrogenation was proposed (Scheme 5). Diene hydoruthenation delivers a nucleophilic allylruthenium complex. The stoichiometric reaction of HXRu(CO)(PPh3)3 (X = Cl, Br) with dienes (or allenes) to form π-allylruthenium complexes has been reported.26 In the case of isoprene 1b,26 cis-stereochemistry between the methyl groups of the resulting π-allyl are observed. Notably, HClRu(CO)(PPh3)3 hydrometates 1,1-dimethylallene to initially form a 1,1-dimethyl substituted π-allylruthenium complex that rearranges to the cis-1,2-dimethyl substituted π-allylruthenium complex,26 suggesting cis-stereochemistry represents a thermodynamic rather than kinetic preference. Intervention of a single geometrical isomer at the stage of the s-allylruthenium intermediate and ensuing transition state for imine addition appears consistent with the relatively high levels of enantioslectivity observed in the asymmetric hydroaminomethylation of isoprene (Scheme 3). Protonolytic cleavage of the amidoruthenium complex derived upon imine addition mediated by isopropanol releases the product of hydroaminomethylation 3b and regenerates the ruthenium hydride to close the catalytic cycle.

Conclusion

In summary, using the concepts of redox-triggered C=X (X = O, N) addition,27 we report the first examples of diene hydroaminomethylation, including asymmetric variants. Specifically, ruthenium catalyzed transfer hydrogenation of 1,3-dienes in the presence of tris(aryl)-hexahydro-1,3,5-triazines results in diene-formaldehyde reductive coupling to deliver homoallylic amines in good yield with complete levels of regioselectivity. While
further optimization is required to enhance performance, these processes define an alternative to classical carboxylative hydroaminomethylation via hydroformylation-reductiveamination, which is presently limited to reactions of non-conjugated olefins. More broadly, these studies contribute to an ever-growing body of catalytic C-C bond formations that merge the characteristics of carbonyl and imine addition with transfer hydrogenation.37

Acknowledgements

The Robert A. Welch Foundation (F-0038), the NSF (CHE-1265504) and the University of Texas Center for Green Chemistry and Catalysis are acknowledged for partial support of this research. The Deutsche Forschungsgemeinschaft (DFG) post-doctoral fellowship program (FR 3555/1-1) is acknowledged for partial support (J.F.).

Notes and references


4 Reppe's pioneering studies employ near stoichiometric loadings of Fe(CO)₅: (a) W. Reppe, Experientia, 1949, 5, 93; (b) W. Reppe and H. Vetter, Liebig. Ann. Chem., 1953, 582, 133.


12 For catalytic reductive coupling of 1,3-dienes with paraformaldehyde, see: (a) T. Smejkal, H. Han, B. Breit and M. J. Krische, J. Am. Chem. Soc., 2009, 131, 10366; (b) A. Köpfer, B. Sam, B. Breit and M. J. Krische, Chem. Sci., 2013, 4, 1876.


