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# Chemo- and regioselective reductive transposition of allylic alcohol derivatives *via* iridium or rhodium catalysis†

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**We report highly chemo- and regioselective reductive transpositions of methyl carbonates to furnish olefin products with complementary regioselectivity to that of established Pd-catalysis. These Rh- and Ir-catalysed transformations proceed under mild conditions and enable selective deoxygenation in the presence of functional groups that are susceptible to reduction by metal hydrides.**

Deoxygenation reactions are important transformations in synthetic organic chemistry, finding applications in areas ranging from biomass conversion to the preparation of complex bioactive molecules.[1,2] Mild, catalytic, chemoselective reductive deoxygenation of alcohols remains underdeveloped owing in large part to the difficulties associated with delivery of hydride equivalents to C–O sigma bonds in preference to C=C, C=O or C–X bonds.[3] Thus classical methods that use stoichiometric additives such as the Barton–McCombie reaction[4] or Mitsunobu reactions with diazene-precursors[5,6] are still widely employed.

With specific regard to allylic substrates, Pd-based strategies have been developed to address some of the limitations associated with selective deoxygenation catalysis. For example, while deoxygenation of allylic alcohols *via* Mitsunobu reaction with diazene precursors NBSH or IPNBSH requires stoichiometric reagents such as diethyl azodicarboxylate (DEAD) (Fig. 1A),[4] Movassaghi and co-workers reported an alternative IPNBSH-mediated reductive transposition using Pd-catalysis (Fig. 1B).[7,8] The regiochemical outcome of the amination follows that expected for Pd-catalysed allylic substitution, generally featuring substrate steric control in the amination of a Pd-allyl species.[9] Under these conditions, terminal olefin products are formed from both branched and linear allylic carbonates after sigmatropic elimination of dinitrogen from a linear monoalkyl diazene (Fig. 1B-1),[10] while both formal $S_N2$ and $S_N2'$ displacement are observed with internal branched substrates (Fig. 1B-2).[7] Similar to Pd-catalysed allylic reductions employing formate,[11,12] generation of the alternative olefin regioisomers is not possible; thus complete regiocontrol of catalytic reductive transposition of allylic alcohol derivatives remains a significant unmet challenge. Furthermore, catalytic and chemoselective diazene-mediated deoxygenation in the presence of other reducible functional groups has not been demonstrated broadly. Herein we report a strategy to address these deficits by employing Ir- and Rh-catalysis (Fig. 1C). Under mild conditions, highly chemo- and regioselective reductive transposition is observed for allylic methyl carbonates. This new method can be considered a direct, catalytic

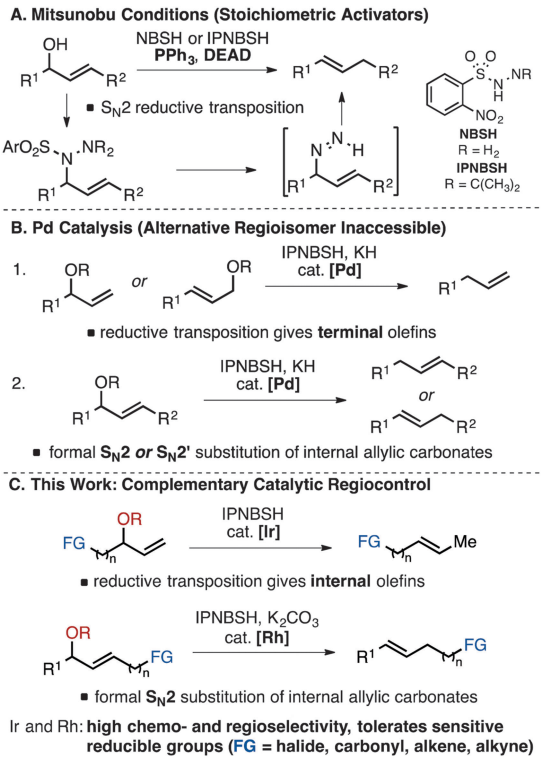


Fig. 1 Overview of diazene-mediated reductive transposition of allylic alcohol derivatives.

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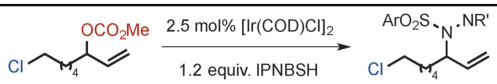
† Electronic supplementary information (ESI) available: Synthetic procedures and characterization data. See DOI: 10.1039/c5cc07993d

Table 1 Effect of reaction parameters on the catalytic, chemoselective allylic amination employing diazene precursors

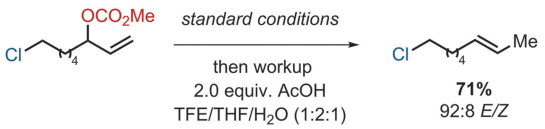



| Entry | Change from the standard conditions | Conv. | Yield (%) |
|---|---|---|---|
| 1 | None | >98 | 91 |
| 2 | $[Rh(COD)Cl]_2$ instead of $[Ir(COD)Cl]_2$ | 8 | <2 |
| 3 | $RuCp^*(MeCN)_3PF_6$ instead of $[Ir(COD)Cl]_2$ | 94 | 10 |
| 4 | THF instead of MeCN | 74 | 15 |
| 5 | $CH_2Cl_2$ instead of MeCN | 61 | 12 |
| 6 | NBSH instead of IPNBSH | 23 | 10 |
| 7 | $CO_2t$-Bu instead of $CO_2$Me | 64 | 44 |

0.05 mmol scale, 24 h, conversions and yields determined by $^1$H NMR using $Bn_2O$ as an internal standard.

alternative to stoichiometric Mitsunobu protocols for deoxygenation of allylic alcohols embedded within functionalised molecules.[13]

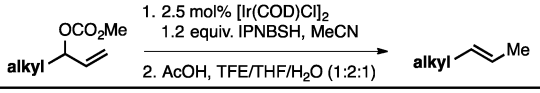
Conditions were optimized such that reactive functionalities, such as aliphatic chlorides are tolerated. Table 1 highlights how simple modifications to the conditions have a significant effect on the selectivity of the transformation when employing bulky diazene precursors.[14,15a] Under optimized conditions employing 2.5 mol% $[Ir(COD)Cl]_2$, the desired branched *N*-alkyl *N*-sulfonyl hydrazone product formed in 91% yield at room temperature with no detectable amount of the linear allylic isomer. Rh- and Ru-based catalysts proved ineffective under these conditions (Table 1, entries 2 and 3). In solvents other than MeCN product yields were significantly lower and formation of the undesired byproducts was observed. The hydrazine reagent NBSH provided suboptimal yields (10%, Table 1, entry 6). Methyl carbonate is the preferred leaving group, as use of alternative alkyl carbonates or a phosphate ester resulted in lower yields.[15b] Finally, *in situ* hydrolysis and sigmatropic rearrangement of the allylic sulfonyl hydrazone at room temperature yielded the desired internal olefin in 71% isolated yield (eqn (1)).[15c] Of note, experiments under similar conditions using ammonium formate as the reducing agent resulted in unselective consumption of the substrate.




(1)

Both simple and functionalised alkyl-substituted allylic carbonates can be converted to the corresponding internal olefins in moderate to excellent yields with very high regioselectivities (Table 2).[16] The reaction is tolerant of substitution β to the carbonate (Table 2, entries 2, 3 and 7), as well as oxygen, nitrogen, and halogen functional groups (Table 2, entries 2–5).[15d] For substrates containing pendant unsaturation in the form of an alkyne, alkene or α,β-unsaturated ester, no over-reduction is observed allowing for facile deoxygenation of polyunsaturated carbonates (Table 2, entries 6–8).[17] In a particularly striking example of chemoselective deoxygenation, methyl carbonate reduction proceeds smoothly in the presence of an allylic acetate group (Table 2, entry 9).[18]

Table 2 Reductive deoxygenation of alkyl substituted allylic carbonates




| Entry | Substrate | Product | Yield (%) |
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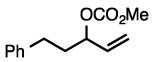
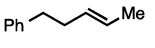
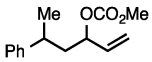
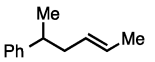
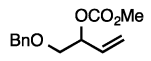
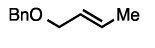
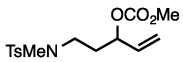
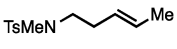
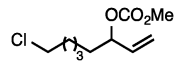
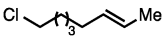
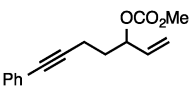
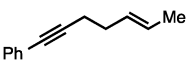
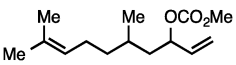
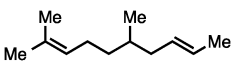
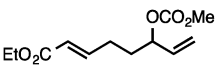
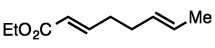
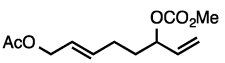
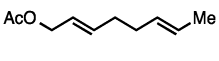
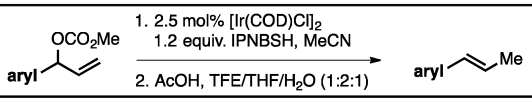
| 1 |  |  | 84 |
| 2 |  |  | 68[a] |
| 3[b] |  |  | 71 |
| 4 |  |  | 88 |
| 5 |  |  | 71 |
| 6 |  |  | 74 |
| 7 |  |  | 57 |
| 8 |  |  | 75 |
| 9[c] |  |  | 65[d] |

Yields are of isolated material. Regioisomer ratios are ≥95 : 5, *E*/*Z* ratios are ≥92 : 8 in all cases. See ESI for details.[a] 91 : 9 regioisomer ratio. [b] 5 mol% $[Ir(COD)Cl]_2$. [c] Allylic acetate *E*/*Z* = 85 : 15 in starting material. [d] Allylic acetate *E*/*Z* = 85 : 15.

Without change to the standard conditions, aryl-substituted allylic carbonates are suitable substrates, allowing for the synthesis of functionalised β-methyl styrenes (Table 3). Electron-rich and electron-poor aryl-substituted carbonates can be deoxygenated under mild conditions. Potentially reactive functional groups that are prone to reduction under radical or metal hydride treatment, such as an aryl bromide and chloride, an allylic ether, ester, nitrile, ketone, and an aryl boronic ester, are tolerated highlighting the excellent chemoselectivity of the reduction.

Allylic carbonates with an internal alkene were resistant to amination with IPNBSH under the standard Ir-catalysed conditions described above. Subsequent optimization, however, revealed that the use of catalytic mixtures of $[Rh(COD)Cl]_2$ and $P(OPh)_3$ with $K_2CO_3$ led to good yields and excellent regioselectivities (Table 4).[15e,f,19] Aryl, alkenyl, alkynyl, and ethereal allylic methyl carbonates can be deoxygenated under these Rh-catalysed conditions, providing a simple and mild strategy for the preparation of sensitive skipped dienes and enynes (Table 4, entries 2 and 4). Allylic carbonates substituted with electron-withdrawing groups, such as an ester or ketone, also undergo amination with high formal $S_N2$-selectivity, and upon reductive transposition, γ-unsaturated carbonyl compounds can be obtained (Table 4 entries 5–8). The reaction tolerates sterically demanding carbonates, such as an α-branched substrate (Table 4, entry 7). Collectively, these results demonstrate an attractive means to convert easily accessible conjugated systems into

Table 3 Scope of reductive deoxygenation of aryl substituted allylic carbonates




| Entry | Substrate | Product | Yield (%) |
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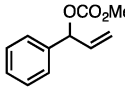
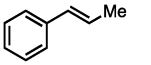
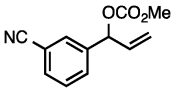
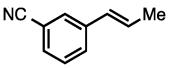
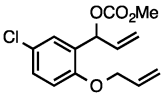
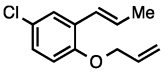
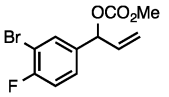
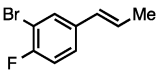
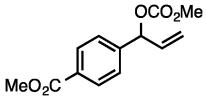
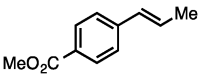
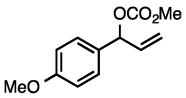
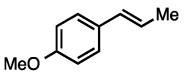
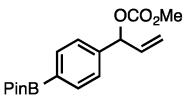
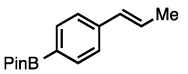
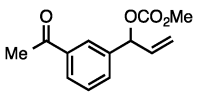
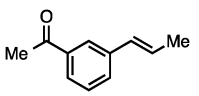
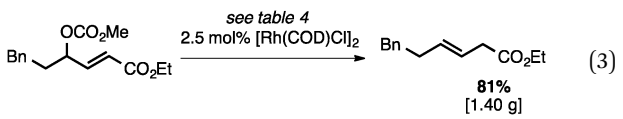
| 1 |  |  | 69 |
| 2 |  |  | 63 |
| 3 |  |  | 71 |
| 4 |  |  | 94 |
| 5 |  |  | 56[a] |
| 6 |  |  | 45 |
| 7 |  |  | 55 |
| 8 |  |  | 77 |

Yields are of isolated material 1.0–0.6 mmol scale. Regioisomer ratios are ≥93 : 7 and *E*/*Z* ratios are ≥95 : 5 unless noted. See ESI for details. [a] 83 : 17 regioisomer ratio.

more valuable 1,4-polyunsaturated compounds that are otherwise difficult to prepare. In keeping with the observation of remarkably high formal $S_N2$ amination selectivity, alkyl-, heteroaryl-, and alkenyl-substituted primary allylic carbonates generate terminal olefin products under the standard Rh-catalysed reaction conditions (Table 4, entries 9–11).

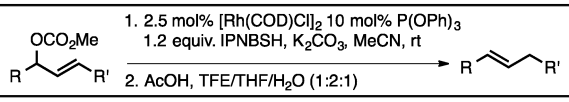
Both of the methods reported herein proceed well on larger scales, as demonstrated by the gram-scale syntheses of a halogenated β-methyl styrene *via* Ir-catalysis (eqn (2)) and a γ-unsaturated ester *via* Rh-catalysis (eqn (3)).[15g]

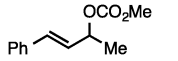
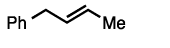
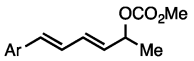
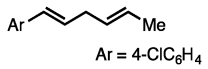
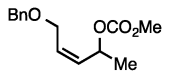
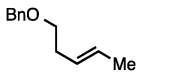
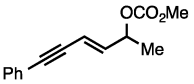
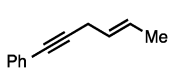
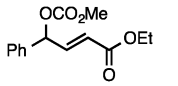
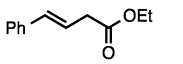
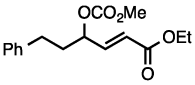
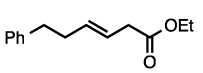
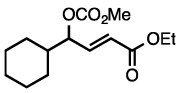
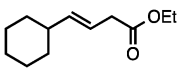
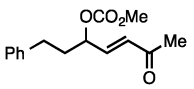
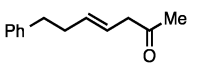
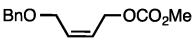
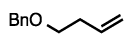
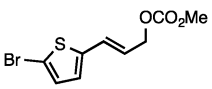
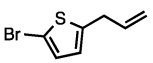

(2)




(3)

Table 4 Rh-catalysed reductive deoxygenation of substituted allylic carbonates




| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1[a] |  |  | 62 |
| 2[a] |  |  | 57 |
| 3[a,b] |  |  | 79 |
| 4[a] |  |  | 64 |
| 5 |  |  | 66 |
| 6 |  |  | 71 |
| 7[b] |  |  | 69 |
| 8 |  |  | 56 |
| 9[b] |  |  | 78 |
| 10[b] |  |  | 52 |
| 11[b] |  |  | 65 |

Yields are of isolated material, 0.7–0.3 mmol scale. Regioisomer ratios are ≥95 : 5 and *E*/*Z* ratios are ≥94 : 6 in all cases.[a] Reaction performed at 40 °C. [b] Using 5 mol% $[Rh(COD)Cl]_2$ and 20 mol% $P(OPh)_3$.

In summary, we have developed new catalytic strategies for the mild and selective reductive transposition of allylic alcohol derivatives employing Ir- or Rh-based catalysts. The deoxygenation process tolerates a wide range of functional groups that are susceptible to radical or hydride reduction and provides complementary regioselectivity to that of Pd-catalysed methodologies. The ability of this method to be used in place of stoichiometric Mitsunobu-type deoxygenation processes should result in widespread appeal.

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## Notes and references

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15 Notes: (*a*) the stable, crystalline reagents NBSH and IPNBSH are commercially available, or readily synthesized on decagram scale; (*b*) for additional optimization data see the ESI†; (*c*) hydrolysis was performed by removal of MeCN prior to addition of THF/TFE/$H_2O$ (2 : 1 : 1) and AcOH, direct addition of TFE/$H_2O$ without THF resulted in ~10% lower yields; (*d*) electron-rich aryl methyl carbonates are prone to rearrangement to the linear isomer, pyridine and quinoline substrates are aminated effectively but undergo reduction with low yield and regioselectivity, cyclic allylic methyl carbonates are not viable substrates, as is generally observed in Ir- and Rh-catalysed allylic functionalization; (*e*) see ESI† for details on optimization of internal allylic substrates; (*f*) these conditions are effective for terminal allylic carbonates, however the reactions proceed with slightly diminished branched/linear selectivity compared to the use of $[Ir(COD)Cl]_2$; (*g*) no glovebox is required for these reactions, see the ESI†.
16 Aside from being useful chemical building blocks, methyl-substituted olefins are found in numerous bioactive molecules, such as cyclosporines, corallopyronins and penibruguieramide A.
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