Unusual Regiodivergence in Metal-Catalysed Intramolecular Cyclisation of γ-Allenols

Jannine L. Arbour, Henry S. Rzepa,* Andrew J. P. White and King Kuok (Mimi) Hii*

Received (in XXX, XXX) Xth XXXXXXXXX 200X. Accepted Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

Different O-heterocycles can be obtained from a common γ-allenol precursor by using Ag, Zn or Sn catalysts; the results were rationalised by molecular modelling.

Intramolecular hydroalkoxylation of γ-allenols can potentially afford 5- or 6-membered O-heterocycles via different mechanistic pathways (Scheme 1). The former (5-exo-trig) cyclisation is more common, and can be obtained using Pt or Au catalysts, including enantioselective reactions, through π-activation of the C=C bond. Conversely, the only known catalytic example of a 6-exo-dig cyclisation was achieved at 130 °C using a lanthanide-amide complex, via C=C insertion into Ln-O. In this Communication, we report an unusual observation in the intramolecular cyclisation of γ-allenols, where the regiochemistry of the process can be altered by using different metal catalysts.

The work initiated with the observation that γ-allenol 1a underwent 5-exo-trig cyclisation in the presence of a catalytic amount of AgOTf to afford 2a. Subsequent screening of metal triflates led to the serendipitous discovery of two catalytic systems that effect complementary 6-exo-dig selectivity (Scheme 2). Under virtually identical conditions, Sn(OTf)2 transformed 1a into benzopyran 4 via tandem C-O/C-C bond formations, while Zn(OTf)2 favoured sequential C-O formations to furnish the acetal structure 5 at a higher temperature (structures 4 and 5 were verified by X-ray crystallography, see Supplementary Information). Although small amounts of 2a were detected in both reaction mixtures (6 and 13%, respectively), 2a, 4 and 5 did not interconvert when left exposed to the other catalysts, suggesting the operation of competitive and irreversible processes.

The regiodivergence of these catalytic systems was similarly observed with substrates 1b and 1c (Scheme 3, Table 1): while AgOTf provided tetrahydrofurans 2b and 2c (entries 1 and 6), corresponding reactions using Sn(II) and Zn(II) triflates afforded tetrahydropyran rings as major products at ambient temperature (entries 2, 4 and 8). In the case of 1b, a mixture of double bond isomers 6a and 6b was obtained, acetal formation was presumably prohibited for steric reasons. Rate of the Sn-mediated reaction was attenuated by replacing the diphenyls in 1a with a cyclohexyl group 1c, such that 5-membered ring formation became competitive (entry 7). The reaction catalysed by Zn(OTf)2 was also sluggish at room temperature, although the larger ring was still preferred (entry 8). At a higher temperature, selectivity for the 6-membered ring product remained unchanged for the system catalysed by Sn(OTf)2 (entries 2 vs 3), while there was a switch in favour of the smaller ring by Zn(OTf)2 (entries 4 vs 5 and 8 vs 9).

Bronsted acid catalysis was investigated by addition of 30 mol% triflic acid to 1a. At room temperature, the formation of 4 was observed in a lower yield (50%, r.t., 23 h) compared to Sn(OTf)2. Likewise, acid-catalysed cyclisation of 1b led to 6a and 6b (1:6 ratio). However, substrate 1c remained inert over 6 days (r.t.). These observations, accompanied by the switch of selectivity for the 5-exo-trig compound at higher temperatures for the Sn and Zn systems, suggest that a H+ catalysed process is not likely to be significant.
Table 1 Cyclisation of γ-allenols 1b and 1c using different catalysts.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor Catalyst</th>
<th>Product</th>
<th>t/h</th>
<th>T/°C</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf</td>
<td>2b</td>
<td>18</td>
<td>r.t.</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>Sn(OTf)2</td>
<td>6a : 6b</td>
<td>28</td>
<td>r.t.</td>
<td>82 (6)</td>
</tr>
<tr>
<td>3</td>
<td>Zn(OTf)2</td>
<td>6a : 6b</td>
<td>34</td>
<td>50</td>
<td>84 (2)</td>
</tr>
<tr>
<td>4</td>
<td>Zn(OTf)2</td>
<td>6a : 6b</td>
<td>28</td>
<td>r.t.</td>
<td>75 (9)</td>
</tr>
<tr>
<td>5</td>
<td>Zn(OTf)2</td>
<td>6a : 6b</td>
<td>34</td>
<td>50</td>
<td>15 (70)</td>
</tr>
<tr>
<td>6</td>
<td>AgOTf</td>
<td>2c</td>
<td>12</td>
<td>r.t.</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>Sn(OTf)2</td>
<td>7</td>
<td>144</td>
<td>35</td>
<td>29 (40)</td>
</tr>
<tr>
<td>8</td>
<td>Zn(OTf)2</td>
<td>7</td>
<td>144</td>
<td>r.t.</td>
<td>45 (9)</td>
</tr>
<tr>
<td>9</td>
<td>Zn(OTf)2</td>
<td>7</td>
<td>36</td>
<td>50</td>
<td>9 (52)</td>
</tr>
</tbody>
</table>

aTypical reaction conditions: γ-allenol (0.4 mmol) in DCE (0.3 mL), catalyst (0.06 mmol., 15 mol%). bIsolated yields after column chromatography. Values in parenthesis denote (isolated) yields of the 5-exo-trig compound. c1c recovered in 25% yield.

DFT-based models were employed to provide a rationale for the observed regiodivergence. Using γ-allenol 1a as substrate, with the counter-ion modelled as triflate (L = OTf, X = SO3) or trifluoroacetate (L = TFA, X = C), the 5-exo-trig transition state (TS1, Scheme 4) resulting in 2a was tested on group 11 metals (Cu, Ag and Au), for which there is reliable experimental data. At the B3LYP/cc-pVDZ level of theory (cc-pVDZ pp for the metal), the activation free energies (ΔG‡) for these are set out in Web-enhanced Table 2. In all cases, ΔG‡ for TS1 (L = TFA) were calculated to be 26.7, 18.1 and 12.2 kcal/mol respectively, commensurate with experimental observations that gold-catalysed reaction occurs at sub-ambient conditions, silver at room temperature, and no reaction was observed with copper under ambient conditions.

Scheme 4 Proposed pathway for 5-exo-trig cyclisation.

Calculated transition normal modes, illustrated as animations in the Web-enhanced Table 1 (M = Cu, Ag, Au) and statically (Figure 1), reveal that C-O bond formation is assisted by concomitant deprotonation of the OH group by the adjacent carbonyl of the ligand, the reaction completing with a protonolysis of intermediate I (TS5). Modifying L = OTf to L = TFA is predicted to reduce the barrier by 1.5 kcal/mol, corresponding to a rate increase of ca. 12-fold at ambient temperature. Indeed, this was verified experimentally: 1a underwent complete cyclisation in the presence of 15% of Ag(TFA) at room temperature within 2 h to furnish 2a in 90% isolated yield (compared to 16 h by AgOTf, Scheme 2).

Possible mechanistic pathways leading to the formation of 6-membered rings are shown in Scheme 5: TS2 was initially proposed as a pathway to product 4, involving electrophilic activation of the allene, followed by aromatic substitution via deprotonation of the Wheland intermediate. Alternatively, the reaction can proceed via TS3, where C-O bond formation is followed by protonolysis, resulting in a cyclic enol ether intermediate, which can be trapped by another molecule of 1a to give 5. An alternative to protonolysis is internal proton transfer (II to III, via TS6) followed by aromatic substitution involving C=O+ as electrophile (TS4), accompanied by synchronous deprotonation of the nascent Wheland intermediate to give 4. The calculations (Web-enhanced Table 1, M = Cu, Ag, Au) reveal that TS1 is lower in free energy than TS2 and TS3 for the group 11 metals, in accord with formation of the kinetic product 2a rather than 4 or 5.

Scheme 5 Proposed pathways for 6-exo-dig cyclisations.

Modelling studies for divalent metals are more complex and subtle, with either tetrahedral (Zn) or hemi-directed (Sn) metal coordinated by two bidentate ligands replacing the linear coordination of the group 11 metals, and the possibility of additional coordination to the metal. Annotated geometries for these are set out in Web-enhanced Table 2. In all cases, TS2 is higher in free energy than the other pathways (TS1 and TS3), and can be discounted from further discussion. For M = Zn, the metal is essentially tetrahedral, achieving this via one Zn-C and three Zn-O bonds (from one bidentate and one monodentate ligands). The remaining oxygen from the monodentate ligand acts as the base for proton removal (Figure 1). TS3 (M = Zn) is now lower in free energy than TS1 (the reverse of that computed for M = Ag), and is assisted by an additional moderate Zn...OH interaction (~2.5-2.6 Å) not present in TS1. With this metal, the product resulting from TS3 (5) is indeed that observed. Conversely, a different geometry is found for TS3 when M = Sn. Rather than a tetrahedral, the hemi-directed metal coordination sphere...
catalysis proceeded via a 5-exo-trig pathway, 6-exo-dig
directed by Lewis acids via divergent pathways: while Ag
Sn-O interaction augmenting the normal coordination. 20
The geometry at the Sn is again notable for a weak (2.90 Å)
mechanistic type to add an example of C-C bond formation.
C-metal bond formation; our observation extends this
Such mechanistic synchronicity has also recently been 15
or
electrophilic aromatic substitution via a mechanism in which 10
possible pathway for C-C bond formation. This represents an
the observed product, we focused on TS4 (Figure 1) as a
kinetic
energies of transition states revealed that kinetic
relative energies of transition states. Only one significant 30
energy of TS4 (L = OTf) to below that of the corresponding
dichloroethane as solvent significantly reduced the relative
computed dipole moments are in the region of 12-15 D 25
than the other transition states, and indeed the (gas phase)
As apparent from Scheme 5, nevertheless, the relative energy of TS4 emerged as higher
appropriately located oxygen atom from one of the ligands.10
monodentate coordination of TFA or OTf, augmented by two
comprises one Sn-C and two Sn-O bonds resulting from
monodentate coordination of TFA or OTf, augmented by two
much weaker (~3.0-3.1 Å) Sn-O interactions (Web-enhanced Table 2). The product observed with the Sn catalyst is not 2a
or 5, but 4. With the high energy TS2 not providing a route to
the observed product, we focused on TS4 (Figure 1) as a
possible pathway for C-C bond formation. This represents an
electrophilic aromatic substitution via a mechanism in which
the loss of aromaticity, implied by formation of a discrete
Wheland intermediate, is minimised by conflating the C-C
bond formation with synchronous deprotonation by an
appropriately located oxygen atom from one of the ligands.10

Such mechanistic synchronicity has also recently been suggested11 for aromatic electrophilic metallations involving
C-metal bond formation; our observation extends this
mechanistic type to add an example of C-C bond formation.
The geometry at the Sn is again notable for a weak (2.90 Å)
Sn-O interaction augmenting the normal coordination.
Nevertheless, the relative energy of TS4 emerged as higher
than that of TS1 or TS3. As apparent from Scheme 5, however, TS4 involves a greater degree of charge separation
than the other transition states, and indeed the (gas phase)
computed dipole moments are in the region of 12-15 D
(compared to 7-10 D for the other transition states). Performing a continuum solvation energy correction for
dichloroethane as solvent significantly reduced the relative
energy of TS4 (L = OTf) to below that of the corresponding
solvated energies of TS1-TS3. Only one significant discrepancy with experimental observation remains; namely
that solvation also reduces the energy of TS4 (M = Zn) to
below that of TS3 (L = OTf).12 Nevertheless, these
calculations do provide an insight into how the variation in
metal coordination can result in differing selectivity by the
metals.

To conclude, regioselective cyclisation of γ-allenols can be
directed by Lewis acids via divergent pathways: while Ag
catalysis proceeded via a 5-exo-trig pathway, 6-exo-dig
cyclisation is favoured by Sn and Zn catalysts. Calculations of
relative energies of transition states revealed that kinetic
control is attained by varying metal geometry and ligand/counterion.

We thank EPSRC and Zambon Advanced Fine Chemicals
(ZaCh Systems S.A.) for studentship support.

Notes and references

Department of Chemistry, Imperial College London, Exhibition Road,
South Kensington, London SW7 2AZ, U.K. E-mail: rzepa@imperial.ac.uk,
mimi.hi@imperial.ac.uk.

† Electronic Supplementary Information (ESI) available: crystallographic
data and cif files for compounds 4 and 5, experimental procedures, and
compound characterization (pdf). Coordinates and animated transition
state normal modes are provided via Web-enhanced tables. See
DOI: 10.1039/b000000x/

2 (a) H. Qian, X. Q. Han and R. A. Widenhoefer, J. Am. Chem. Soc.,
2004, 126, 9536; (b) Z. B. Zhang, C. Liu, R. E. Kinder, X. Q. Han,
3 (a) G. L. Hamilton, E. J. Kang, M. Mba and F. D. Toste, Science,
2007, 317, 496; (b) Z. B. Zhang and R. A. Widenhoefer, Angew.
4 Endo-cyclisation of activated allenols was achieved using 1.5
equivalents of i-ButOK: C. Mukai, M. Ohta, H. Yamashita and S.
5 X. H. Yu, S. Seo and T. J. Marks, J. Am. Chem. Soc., 2007, 129,
7244.
6 For our prior work, see: (a) L. A. Adrio and K. K. Hii, Chem.
Commun., 2008, 2325; (b) P. H. Phua, S. P. Mathew, A. J. P. White,
13, 4602; (c) J. G. Taylor, N. Whittall and K. K. Hii, Org. Lett.,
2006, 8, 3561; (d) J. G. Taylor, N. Whittall and K. K. Hii, Chem.
7 Regiodivergent (5-exo vs 7-exo-trig) cyclisation of γ-allenols had
been reported, but different protecting groups were deployed on the
precursors: B. Alcaide, P. Almendros and T. M. del Campo, Angew.
8 Reactions were reported by using 1.2-2 eq. of AgNO3: P. Audin,
9 After the submission of this manuscript, triflic acid-catalysed reactions of 1a to 4 was reported to proceed in refluxing CH2Cl2 (20
mol\%, 5 h, 80% yield). The crystal structure of 4 was also reported:
are grateful to Prof. Akiyama for bringing the reference to our
attention.
10 Retention of ring aromaticity despite having 4-coordination at one
of the ring carbons is a known phenomenon, see: (a) B. J. Wehrschulte,
Solari, F. Musso, E. Gallo, C. Fioriani, N. Re, A. Chiesi-Villa and C.
Rizzoli, Organometallics, 1995, 14, 2265. (c) N. Choi, P. D. Lickiss,
M. McPartlin, P. C. Masangane and G. L. Veneziani, Chem.
2008, 130, 10848 and references cited therein.
12 Advances in computational solvation methodologies will allow
solvation potential surfaces to be more effectively explored and the
origins of such discrepancies probed; D. M. York and M. Karplus,

Fig. 1 Calculated normal transition mode for the cyclisation of 1a: TS1 (left, M = Ag), TS3 (middle, M = Zn) and TS4 (right, M=Sn), L = OTf.