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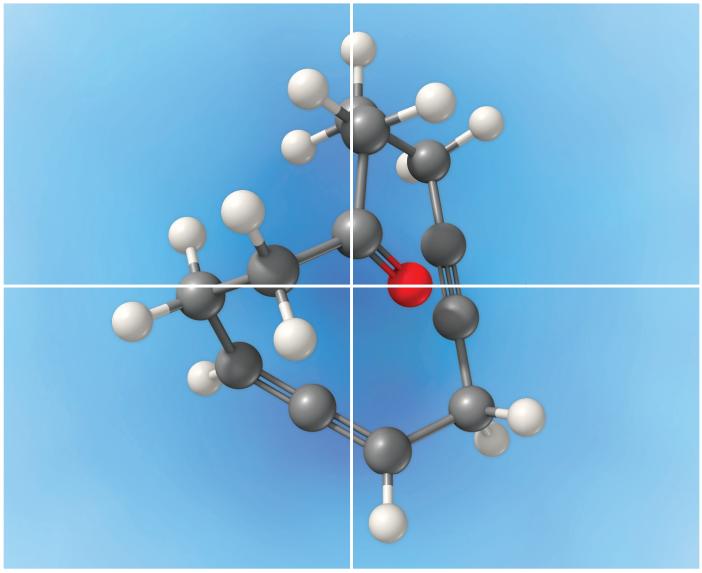

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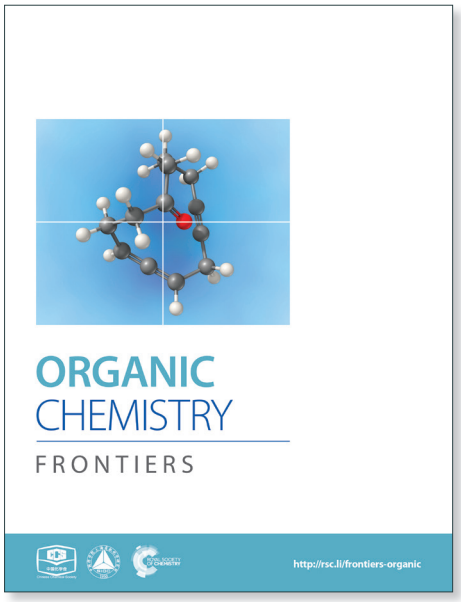

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ARTICLE TYPE

$Hg(OAc)_2$ mediated highly regio- and/or diastereoselective allylic *tert*-acetylation of olefins

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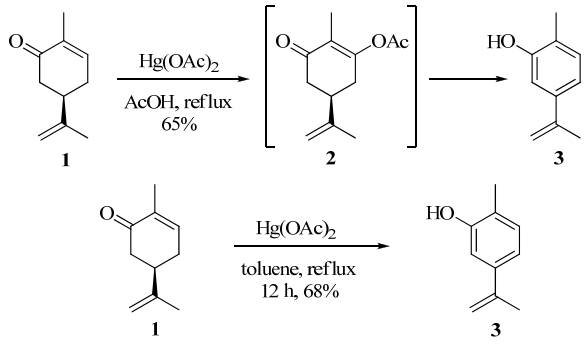
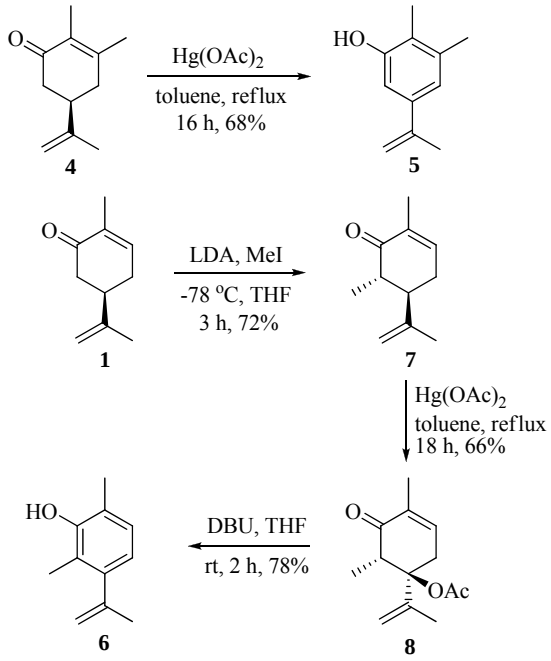
Isolation of reaction intermediate lead to mechanistic investigation of known $Hg(OAc)_2$ mediated aromatisation reaction of carvone. We propose different mechanism for this reaction than the earlier proposed mechanism. The reaction was further exploited for the highly regio- and/or diastereoselective allylic oxidation of geminally disubstituted olefins to allylic *tert*-acetates and applied in the total synthesis of andirolactone.

With our ongoing research for the development of novel reactions and methods for the synthesis of highly substituted indenes,[1] we came across the literature report, where Treibs[2] had done aromatisation of carvone **1** using stoichiometric $Hg(OAc)_2$. We thought of exploiting this reaction for the synthesis of substituted aromatic derivatives which are otherwise not trivial to make by conventional methods.[3] In the original report Treibs[2] have reported aromatisation of carvone **1** using stoichoimetric $Hg(OAc)_2$ in acetic acid reflux condition. Treibs proposed that carvone **1** on treatment with $Hg(OAc)_2$ under acidic conditions might be forming intermediate **2** which on further elimination forms the phenol derivative **3** (Scheme 1). After screening different solvents, temperature, we found that carvone **1** could be aromatised in 68% yield by stoichiometric $Hg(OAc)_2$ under toluene reflux conditions without using AcOH or any other acid.[4] After the standardisation of reaction, we next turned our attention towards the mechanism of the reaction. As Treibs proposed that compound **2** could be the intermediate in aromatisation reaction, it was thought that substitution at 3-position of carvone **1** might stop its aromatisation as per the proposed mechanism. So to validate the proposed mechanism, we treated 3-methylcarvone (**4**) with $Hg(OAc)_2$ under toluene reflux conditions. Surprisingly

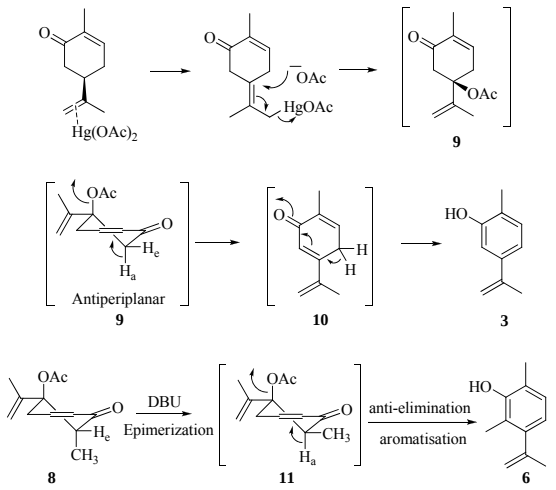


Scheme 1 Mercury acetate mediated aromatisation of carvone.



Scheme 2 Aromatisation of carvone derivatives.

compound **4** under these reaction conditions aromatised to furnish the compound **5** in 68% yield, suggesting that proposed mechanism might not be correct. All our efforts to isolate the intermediate of carvone aromatisation reaction failed but interestingly, in an attempt to make substituted aromatic compound **6**, when we treated *trans*-6-methylcarvone (**7**) with $Hg(OAc)_2$ under toluene reflux conditions, instead of isolating corresponding aromatic compound **6**, we isolated the compound **8** having acetate group at C-5 position of methylcarvone **7** as the only diastereomer in 66% yield. The structure of the compound **8** was established by spectroscopic analysis (IR, ^1H, ^{13}C NMR and HRMS). Treatment of compound **8** with catalytic DBU in CH_2Cl_2 furnished the aromatised product **6** in 78% yield presumably via epimerization, further confirming the structure of compound **8**. The stability of compound **8** under reaction conditions could be explained by *syn* and *anti* elimination chemistry. Carvone **1** on treatment with $Hg(OAc)_2$ generates the intermediate **9** *in situ*, which then undergoes facile anti elimination, since one of the hydrogens α to the keto group is antiperiplanar to the acetate group, to give the dienone **10** under reaction conditions. The

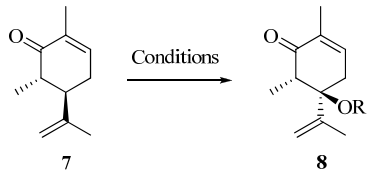


Scheme 3 Proposed mechanism for carvone aromatisation.

dienone **10** on further isomerisation yields the phenol **3**. But *trans*-6-methylcarvone **7** on reaction with $Hg(OAc)_2$ forms tertiary acetate **8** as shown in scheme 3. The difference between intermediate **9** and **8** is that, in case of **9**, there is a hydrogen antiperiplanar to acetate group which undergoes facile E2 elimination, so it is not possible to isolate the intermediate **9**. Since tertiary acetate **8** does not have the acidic proton antiperiplanar to the acetate group, elimination does not takes place and so in this case the intermediate **8** is isolable unlike the case of **9**.

After establishing the mechanism of the aromatisation reaction and impressed by the diastereoselectivity and regioselectivity of this reaction, we thought of exploiting this reaction for the allylic acetylation of olefins. Although allylic oxidation of olefins by mercury acetate is well documented in literature,[5] due to poor selectivity, yield and its toxicity, later it was replaced by more efficient catalytic methods using palladium based catalysts. We also screened different palladium,[6] copper[7] and selenium[8] catalysts for the same transformation, but unfortunately it didn't

Table 1 Screening of catalysts for oxidation of methyl carvone **7** to **8.**



Entry	Conditions	R	Yield(%)[a]
1	$Pd(OAc)_2$, BQ, DMSO, AcOH	-Ac	nil[b]
2	$Pd(TFA)_2$, 2-methoxyacetophenone, BQ, AcOH	-Ac	nil[b]
3	CuBr, $PhCO_3{}^tBu$, toluene	-Bz	nil[c]
4	$Cu(OAc)_2$, $PhCO_3{}^tBu$, toluene	-Bz	nil[b]
5	CuCl, $PhCO_3{}^tBu$, toluene	-Bz	nil[c]
6	SeO_2, ^tBuOOH, DCM	-H	6
7	SeO_2, H_2O_2	-H	8
8	$Hg(OAc)_2$, toluene	-Ac	66

[a] Isolated yield. [b] decomposition of starting material observed. [c] Recovered starting material.

Table 2 Regioselective allylic acetylation of optically active cyclohexene derivatives[a]

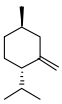
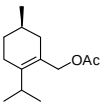
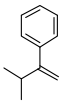
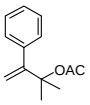
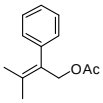
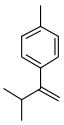
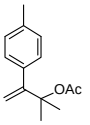
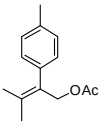
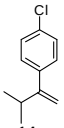
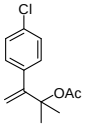
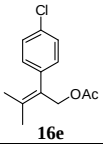
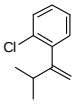
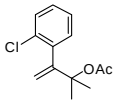
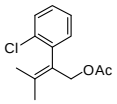
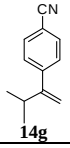
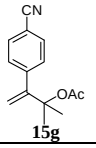
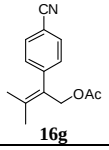
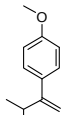
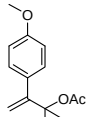
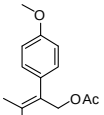
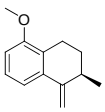
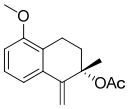
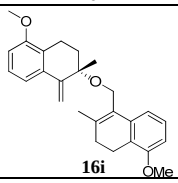
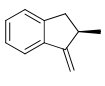
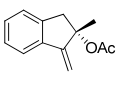
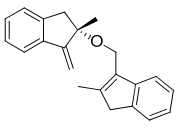
Entry	Substrate	Product	de %	Yield (%)
1	**12a**	**13a**	>99	64
2	**12b**	***ent*-13a**	>99	66
3	**12c**	**13c**	>99	64
4	**12d**	***ent*-13c**	>99	67

[a] Isolated yields, 1.2 eq of Mercury acetate was used.

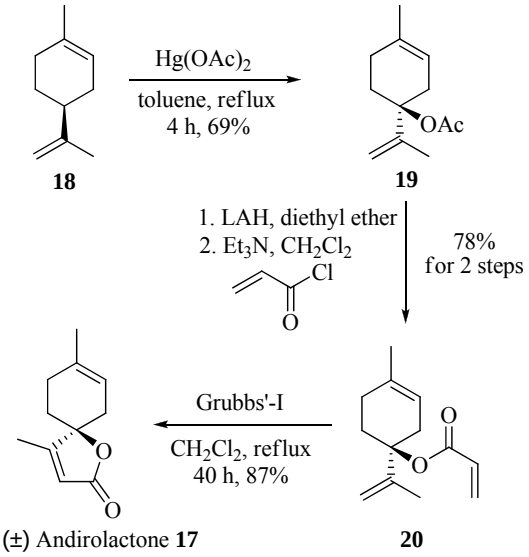
generate any allylic oxidation product, instead in most of cases we observed very poor yield with multiple spots on tlc or recovered the starting material in some cases (Table 1). Considering the fact that currently there is no method available in the literature for such selective allylic *tert*-acetylation, we thought of testing the generality and substrate scope of this reaction. To our delight, reaction showed broader substrate scope and generated *tert*-acetylation product in highly regioselective manner (Table 2). Diastereomers **12a** and **12b** on independent treatment with $Hg(OAc)_2$ in refluxing toluene furnished compound **13a** and its optical antipode ***ent*-13a** in excellent diastereoselectivity. In both **12a** and **12b** approach of incoming acetate group is controlled by adjacent methyl group, hence in **12a** and **12b**, it generates *trans* isomers with respect to acetate and the chiral methyl group. Thus, we were able to a generate pair of enantiomers (**13a** and ***ent*-13a**) from two diastereomers (**12a** & **12b**). In the case of menthene **14b**, we were not able to isolate the expected *tert*-acetate compound, instead it furnished allylic secondary acetate **15b** as the only product in 71% yield. We also explored various styrene derivatives for the allylic acetylation reaction (Table 3). All styrene derivatives generated the expected acetylation product in moderate yield (56-74%) along with rearranged secondary acetates (6-12%). Tetralin and indene derivatives (Entry **14i** and **14j**) afforded acetates **15i** and **15j** in 60% and 59% yield respectively along with minor amount of dimers **16i** and **16j**.

Finally, this reaction was applied for the total synthesis of natural product andirolactone (**17**). In 1987, Avcibasi et al., isolated a spirocyclic butenolide terpenoid andirolactone (**17**) with potential biological and medicinal properties, from the

Table 3 Regioselective allylic oxidation of geminally disubstituted olefins to allylic *tert*-acetates[a]

Entry	Substrate	Product		Ratio (A:B)	Yield %
		Major (A)	Minor (B)		
1	 **14a**	 **15a**	 **16a**	5:1	67
2	 **14b**	 **15b**	-	-	71
3	 **14c**	 **15c**	 **16c**	11:1	70
4	 **14d**	 **15d**	 **16d**	9:1	78
5	 **14e**	 **15e**	 **16e**	10:1	73
6	 **14f**	 **15f**	 **16f**	10:1	77
7	 **14g**	 **15g**	 **16g**	11:1	81
8	 **14h**	 **15h**	 **16h**	9:1	71
9	 **14i**	 **15i**	 **16i**	5:1	72
10	 **14j**	 **15j**	 **16k**	6:1	68

[a] Isolated yields, 1.2 eq of Mercury acetate was used.



Scheme 4 Total synthesis of Andirolactone **17**.

wood of libanese cedar (*Cedrus libanotica*).[9] To date there are 7 total syntheses of andirolactone are reported in the literature.[10] Herein we report the concise synthesis of andirolactone. It was envisioned that andirolactone (**17**) could be synthesized from limonene **18** by its regioselective *tert* allylic oxidation, reduction of ester, which leaves behind tertiary alcohol, followed by treatment with acryloyl chloride and finally ring closing metathesis (RCM) of the diene thus generated. So limonene **18**, having five allylic positions available for oxidation on treatment with $Hg(OAc)_2$ in refluxing toluene generated *tert* acetate **19** in 69% yield (83% brsm) in highly regioselective manner. Reduction of acetate **19** to tertiary alcohol, followed by treatment with acryloyl chloride gave the diene intermediate **20**. RCM of diene **20** using 5 mol% of Grubbs' first generation catalyst afforded the natural product andirolactone (**17**) in 87% yield (46.8% overall yield) (Scheme 4).

Conclusions

In summary, we have developed a novel, highly regio- and/or diastereoselective tertiary allylic acetylation of geminally disubstituted olefins using $Hg(OAc)_2$. Reaction was applied in total synthesis of andirolactone with very good overall yield. Although the catalyst used in above mentioned transformation is not the desired one due to its toxicity, emphasis of this manuscript is on novel transformation to regioselectively formation of *tert*-acetates which gives chance to modify/change to better catalyst in future investigations.Presently efforts are going on in our lab to replace toxic $Hg(OAc)_2$ by better catalyst for this transformation.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (a) D. H. Dethe and G. Murhade, *Org. Lett*., 2013, **15**, 429; (b) D. H. Dethe and G. M. Murhade, *Chem. Commun.,* 2013, **49**, 8051.

2 Wilhelm Treibs, *Justus Liebigs Annalen der Chemie*, 1953, **581**, 59.

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4 As Mercury(II)acetate is highly toxic, and it releases toxic Mercury in the reaction medium, proper care must be taken while handeling it and performing the reaction.

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