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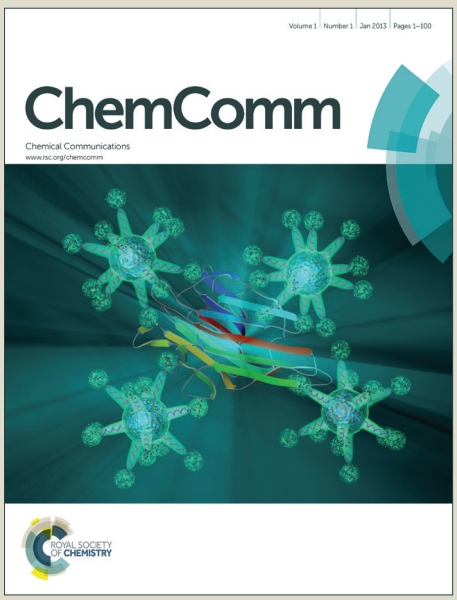

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An efficient route to highly enantioenriched tetrahydroazulenes and β-tetralones by desymmetrization reactions of δ,δ-diaryldiazoaceto-acetates

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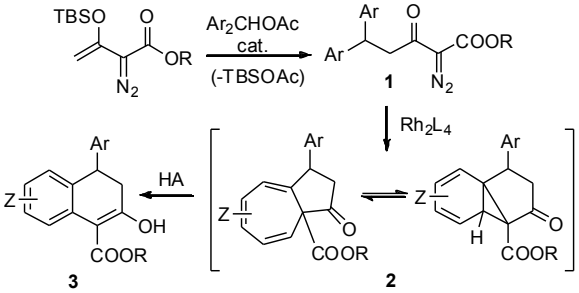
A highly stereoselective desymmetrization reaction of δ,δ-diaryl-α-diazo-β-ketoesters catalyzed by chiral dirhodium carboxylates forms aromatic cycloaddition products in up to 97% ee.

Addition, insertion, and ylide transformations of catalytically generated metal carbenoid intermediates are well-established as useful synthetic methodologies.[1] Initiated by reactions with diazo compounds, these processes can be highly stereoselective.[2] Intramolecular reactions with diazoacetates, α-diazoketones, and diazoacetamides generally exhibit remarkable enantioselectivity in reactions catalyzed by chiral dirhodium(II) compounds,[3] and similar or improved stereocontrol is achieved in reactions with donor-acceptor diazo compounds.[4] However, acceptor-acceptor diazo compounds that include diazoacetoacetates have not shown high enantioselectivities in metal carbene reactions with either chiral dirhodium(II) or copper(I) catalysts.[5,6] Although these acceptor-acceptor diazo compounds are among the most stable, their metal carbene intermediates are considerably less stable and less selective in their chemical reactions.



Scheme 1 Synthesis and aromatic cycloaddition reactions of δ,δ-diaryl-α-diazo-β-ketoesters (**1**)

We have recently been able to access δ,δ-diaryl-α-diazo-β-ketoesters (**1**) by a simple one-step Lewis acid catalysed reaction between enoldiazoacetates and benzhydryl acetates.[7] These products are suitably constructed for benzylic insertion, aromatic substitution, or aromatic cycloaddition (Buchner reaction).[1a] Since initial reactions with rhodium acetate showed preference for aromatic cycloaddition (Scheme 1), we considered whether chiral catalysts could achieve highly enantioselective reactions. A comprehensive literature survey of enantioselective aromatic cycloaddition from all diazo compounds, including diazoacetates and diazoketones,[8] showed that, except with one highly substituted diazoketone having a resulting % ee of 95%,[8c] the highest % ee values were in the low 80s. When the two aryl groups of **1** are identical, they are enantiotopic; and this system is constructed for desymmetrization that, although having considerable success in C-H insertion reactions,[9] has not been particularly effective for metal carbene addition reactions.[10] We wish to report that desymmetrization of δ,δ-diaryl-α-diazo-β-ketoesters occurs with exceptional enantiocontrol and in high yield and that acid catalysed rearrangement of the aryltetrahydroazulenes forms δ–aryl-β-tetralones without loss in yield or selectivity.

Reaction of methyl 2-diazo-3-oxo-5,5-diphenylpentanoate **1a** (Ar = Ph, R = Me) with $Rh_2(OAc)_4$ in refluxing CH_2Cl_2 gave a mixture of aromatic cycloaddition (**2a**) and substitution (**3a**) products in a 4:1 ratio that, following treatment with TFA, formed only the substitution product.[7] The initially formed substitution product could have arisen by either electrophilic aromatic substitution of the intermediate metal carbene or by rearrangement of **2a** following aromatic cycloaddition with $Rh_2(OAc)_4$ acting as a Lewis acid to catalyze the transformation to **3a** from **2a**.

We investigated the outcome of intramolecular reactions of **1a** with a broad selection of chiral dirhodium catalysts (Table 1) under the same conditions as were used for the reaction with rhodium acetate. Isolated product yields following chromatography were very high. Chiral dirhodium carboxamidate catalysts[3] were inactive towards diazoacetoacetates under these conditions. Use of the DOSP ligated dirhodium carboxylate catalyst[11] gave a high yield of product but negligible enantioselectivity. However, the imide-ligated dirhodium carboxylate catalysts developed by Hashimoto and coworkers[12] were effective in providing enantiocontrol.

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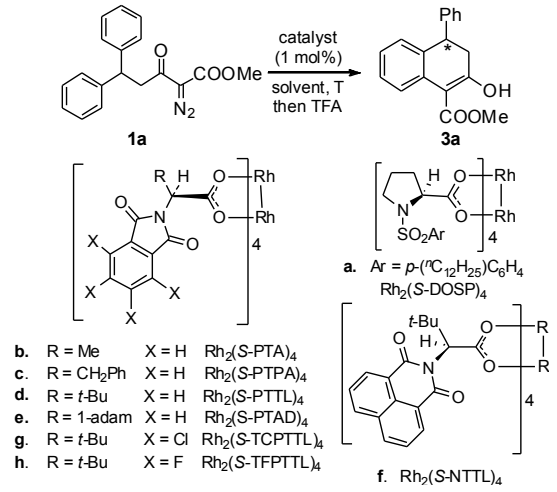
Increasing the size of the alkyl substituent on the phthalimide ligand template provided increases in enantioselectivity, and further enhancement was achieved by electron withdrawal from the phthalimide ring. Lowering the temperature to 0°C increased selectivity as did changing to a less polar solvent. In order to perform the reaction at 0℃ in a cyclohexane (mp 6.5 °C) medium, other solvents were added which resulted in an improvement in enantioselectivity to 90% *ee* (entries 15-17). However, decreasing the temperature further did not benefit enantiocontrol in the reaction. No reaction of **1a** occurred with catalysis by Cu(I)-*t*-BuBox overnight at 0 °C.

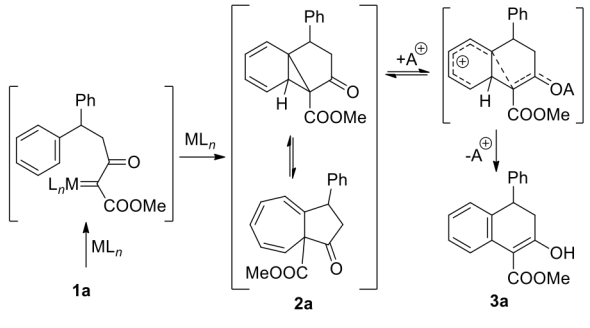
Table 1 Optimization of reaction conditions [a]



Entry	Catalyst	Solvent	T [℃]	Yield [b] [%]	*ee* [%] [c]
1	Rh_2[(*S*)-DOSP]$_4$ **(a)**	DCM	42	89	-3
2	Rh_2[(*S*)-pta]$_4$ **(b)**	DCM	42	90	38
3	Rh_2[(*S*)-ptpa]$_4$ **(c)**	DCM	42	89	34
4	Rh_2[(*S*)-pttl]$_4$ **(d)**	DCM	42	90	52
5	Rh_2[(*S*)-ptad]$_4$ **(e)**	DCM	42	90	55
6	Rh_2[(*S*)-nttl]$_4$ **(f)**	DCM	42	90	60
7	Rh_2[(*S*)-tcpttl]$_4$ **(g)**	DCM	42	92	64
8	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	DCM	42	91	70
9	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	DCM	0	91	79
10	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	TBME	0	84	84
11	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	C_6H_{12} [d]	r.t.	90	87
12	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	trifluorotoluene	0	89	83
13	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	toluene	0	89	83
14	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	DMB	0	89	88
15	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	C_6H_{12}:TBME (15:1)	0	87	90
16	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	C_6H_{12}:DMB (10:1)	0	89	90
17	Rh_2[(*S*)-tfpttl]$_4$ **(h)**	C_6H_{12}:toluene (15:1)	0	90	90

[a] Reactions were carried out over 3-6 h on a 0.10 mmol scale: **1a** (0.1 mmol) in 0.7 mL solvent was added *via* syringe pump to a solution of catalyst (0.001 mmol) in 0.3 mL of solvent, followed by in situ treatment with TFA (0.1 mmol, 1.0 equiv.) for 1 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (see ESI for details). [d] Cyclohexane.

The optimized reaction conditions were employed to evaluate if any of the substitution product formed prior to treatment with TFA arose from direct substitution rather than aromatic cycloaddition/-rearrangement. Using 1 mol% Rh_2[(*S*)-tfpttl]$_4$ a mixture of **2a** and **3a** were obtained in a 1:3.2 ratio, then separated chromatographically and their % ee determined: **2a** (18% isolated yield, 90% ee after conversion to **3a** with TFA) and **3a** (74% isolated yield, 90% ee). These results strongly suggest that all of **3** is formed by aromatic cycloaddition/rearrangement rather than by electrophilic aromatic substitution by the electrophilic metal carbene. Although the chromatographic separation of **2a** from **3a** on silica gel increased the **2a:3a** ratio from 1:2 to 1:3, the major source of catalyst for conversion of **2a** to **3a** (Scheme 2) is the dirhodium catalyst.

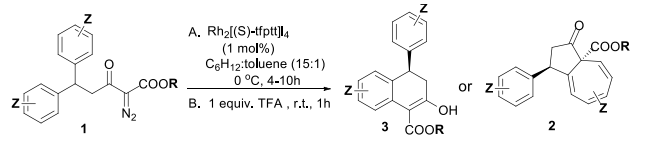


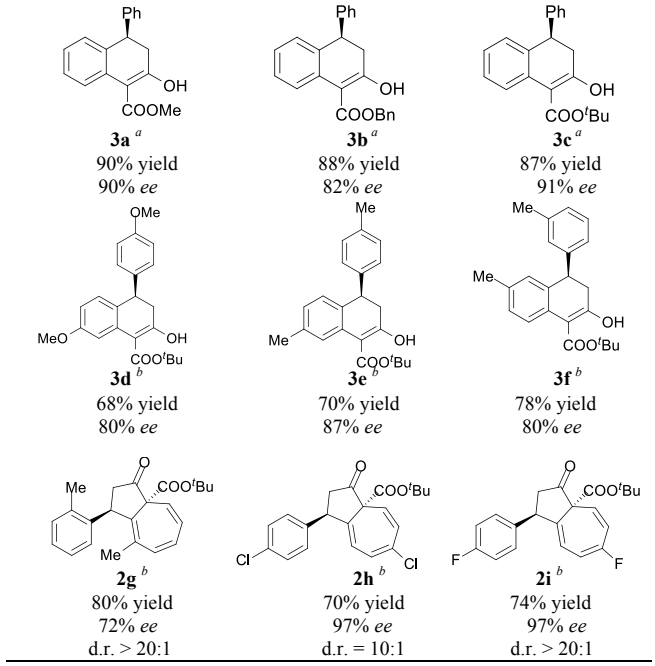
Scheme 2 Acid catalysed conversion of tetrahydroazulenes to β-tetralones

We then explored the scope of this process with representative symmetrical δ,δ-diaryl-α-diazo-β-ketoesters that could be prepared from enoldiazoacetates and benzhydryl acetate.[7] The results from these investigations, performed under optimized conditions with Rh_2[(*S*)-tfpttl]$_4$, are given in Table 2 with assigned stereochemistry based on X-ray and spectral analyses. In general, the reactions with different δ,δ-diaryldiazoesters proceeded smoothly to give the corresponding products with good to excellent enantioselectivities, especially for those that have electron-withdrawing substituents (Z). Use of the benzyl ester (**1b**) resulted in reduced enantioselectivity, but with the *tert*-butyl ester (**1c**) slightly higher stereocontrol for the β-tetralone product was observed. The electronic nature of aryl group substituents had a significant influence on the products that were formed. Whereas **1a-1c** formed mixtures of aryltetrahydroazulenes (**2**) and δ–aryl-β-tetralones (**3**) from reactions catalysed by Rh_2[(*S*)-tfpttl]$_4$ and required treatment with TFA to complete the conversion to **3a-c**, aryltetrahydroazulene products having electron donating groups (Me and OMe), formed from **1d-f** by aromatic cycloaddition, were easily converted to the corresponding β-tetralones **3d-f** on silica gel during chromatography without treatment with TFA. The aryltetrahydroazulenes formed from **1h,i** that have electron withdrawing groups were stable on silica gel and were characterized directly without conversion to β-tetralone products. Reactants with electron-withdrawing chloro and fluoro substituents (Z) para on the benzene ring (**1h,i**) afforded tetrahydroazulenes **2h,i** as the sole products in 97% *ee*. Lower enantiomeric excesses were found with reactants whose aromatic rings were substituted with electron-donating groups (**1d-f**), The position of the methyl substituent on the aryl group was also examined to determine the influence of steric hindrance on enantioselectivity. Lower enantiomeric excess was found with the *meta*-methyl substrate than with the *para*-isomer, but only one regioisomer (from cycloaddition to the 1,6-position) was formed, and the *ortho*-methyl substrate also produced only one regioisomer (**2g**) but with the lowest enantiomeric excess (72%) in the series.

High trans diastereoselectivities were found for **2g-I** indicating that cycloaddition occurs onto the face of the arene that is away from the non-reacting arene.

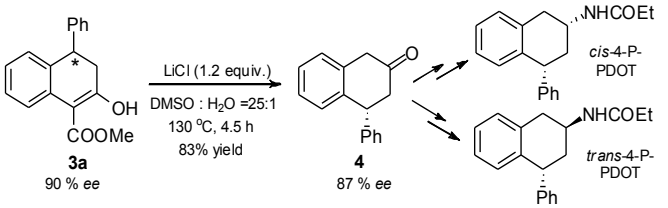
Table 2 Substrate scope of desymmetrization reactions with symmetrical δ-diaryl diazoesters





[a] Reactions were carried out over 4 h on a 0.15 mmol scale at 0 °C: **1a-c** (0.15 mmol) in 1.2 mL solvent was added *via* syringe pump to a solution of Rh_2[(*S*)-tfpttl]$_4$ catalyst (0.0015 mmol) in 0.4 mL of solvent, followed by in situ treatment with TFA (0.15 mmol, 1.0 equiv.) for 1 h. [b] Reactions were carried out over 4-10 h on a 0.15 mmol scale at 0 °C: **1d-i** (0.15 mmol) in 1.2 mL solvent was added *via* syringe pump to a solution of catalyst (0.0015 mmol) in 0.4 mL of solvent.

β-Tetralone[7] **3a** resembles biologically active tetralin natural products, such as the calamenenes,[13] as well as synthetic intermediates used to prepare drug-like molecules.[14] To further demonstrate the utility of this asymmetric aromatic cycloaddition/-rearrangement methodology, β-tetralone **3a** was decarboxylated in the presence of 1.2 equivalent LiCl at 130 °C to afford (*R*)-4-phenyl-3,4-dihydronaphthalen-2(1*H*)-one **4** in 83% yield with a slight loss of optical purity (Scheme 3). This structural motif has played an essential role in synthesis of *cis*- and *trans*-4-P-PDOT[15] (4-phenyl-2-propionamidotetralin), which has been employed to discriminate the role of MT_1 and MT_2 receptors in melatonin-mediated effect.[16]



Scheme 3. Decarboxylation of the chiral β-tetralone **3a**

The absolute configuration of **3a-f** was determined to be *R* by comparing the optical rotation of **4** to that of the previously prepared compound, obtained by optical resolution of the racemic **4**.[15] In addition, the major diastereoisomer of **2h** as well as its absolute configuration (1*R*,3a*S*) were determined through single-crystal X-ray analysis (Figure 1).[17]

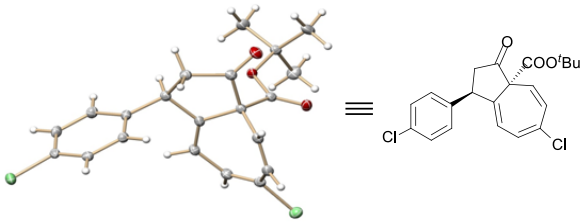


Figure 1 X-ray crystal structure of **2h**. ORTEP view showing stereo-chemistry of **2h**. Elipsoids are shown at 30% probability.

In summary, a facile, efficient and highly stereoselecive desymmetrization of δ,δ-diaryl diazoacetoacetates has been developed by using chiral dirhodium carboxylate catalysts. This study provides a two-step process for the formation of 4-aryltetralones in high optical purity, and with aryltetrahydroazulene enantioselectivities up to 97% *ee*. The desymmetrization methodology has overcome the barrier for high enantiocontrol that is associated with acceptor-acceptor diazoacetoacetates and the Buchner reaction.[18] Furthermore, the utility of β-tetralones formed by this methodology to prepare precursors to 4-P-PDOT has been demonstrated. Reported as an efficient methodology for the construction of β-tetralones only 30-years ago,[19] the intramolecular Buchner reaction has been widely used.[20] Studies are onging to broaden the scope of the Buchner reaction and to investigate the feasibility of chiral dirhodium catalysts for other diastereoselective and enantioselective desymmetrization reactions of acceptor-acceptor diazo compounds.

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