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Catalytic Enantioselective Tandem Carbonyl Ylide Formation-Cycloaddition

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Abstract: Catalytic enantioselective tandem carbonyl ylide formation-cycloaddition of α-diazo-β-ketoesters **1** (R = alkyl, n = 1,2) using 1 mol% $[Rh_2(S\text{-DOSP})_4]$ **2** in hexane at room temperature to give the cycloadducts **3** in good yields and up to 53% *ee* are described.
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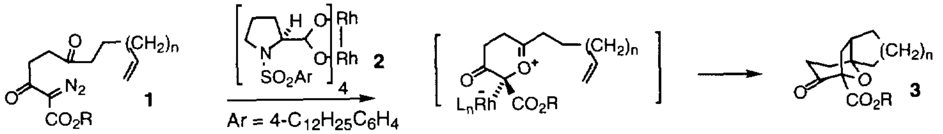
In connection with our interest in Rh(II)-catalysed tandem carbonyl ylide formation-cycloaddition of diazocarbonyl compounds,[1] we communicate here an enantioselective version of this process. Although significant progress has been made in transformations of diazocarbonyl compounds involving enantioselective C=C, C-H or X-H (X = N, O, Si) insertions using chiral, non-racemic Rh(II) catalysts,[2,3] to our knowledge there are no reported examples of enantioselective tandem carbonyl ylide formation-cycloaddition, despite the potential utility of such an asymmetric transformation.[4] Unlike enantioselective insertion, where an intermediate rhodium carbenoid can directly exert an influence on selectivity, it could be argued that once an ylide is formed the catalyst is not involved in the subsequent cycloaddition and asymmetric induction would be unlikely. However, Padwa and co-workers recently observed Rh(II) catalyst-dependent changes in regiochemistry during intramolecular cycloaddition following carbonyl ylide formation.[5] Also, McKervey and co-workers have reported that asymmetric induction is possible in [2,3] sigmatropic rearrangements following oxonium ylide generation from diazocarbonyl compounds using chiral, non-racemic Rh(II) catalysts.[6] One important factor which could influence asymmetric induction might be the rate of cycloaddition of a carbonyl ylide, since a presumed requirement for any asymmetric induction would be that cycloaddition is faster than catalyst decomplexation from the ylide. We therefore first examined an α-diazo-β-ketoester **1** (R = Et, n = 1)[7] designed to undergo intramolecular cycloaddition with a simple terminal alkene, as a closely related system **1** (CO_2R = H, n = 1) had previously been shown to undergo intramolecular cycloaddition faster than intermolecular cycloaddition of the ylide with the highly reactive dipolarophile DMAD.[8]



Treatment of α-diazo-β-ketoester **1** (R = Et, n = 1) with $Rh_2(5R\text{-MEPY})_4$ in CH_2Cl_2 gave a similar yield of cycloadduct **3** (R = Et, n = 1, 75%)[9] to that found using $Rh_2(OAc)_4$ (73%), however no specific rotation was observed. The first indications of asymmetric induction (~8% *ee*)[10] were observed in CH_2Cl_2 with the Rh catalysts derived from *N*-[(4-nitrophenyl)sulphonyl]proline and *N*-[(4-dodecylphenyl)sulphonyl]proline [Rh_2(*S*-DOSP)$_4$] **2**.[11] In line with other asymmetric transformations using Rh_2(*S*-DOSP)$_4$ **2**[2,11] a significant increase in *ee* was observed on switching to a hydrocarbon solvent. Within the scope of the present study, reaction in hexane using 1 mol% Rh_2(*S*-DOSP)$_4$ **2** at 28 °C was found to be optimal in terms of *ee* to give the cycloadduct **3** [R = Et, n = 1, 76%, 53% *ee*, $[\alpha]^{20}_{D}$ +15.8 (*c* 1 in $CHCl_3$), predominant sense of asymmetric induction not known]. Yields of the cycloadduct **3** steadily improved as the reaction was carried out at increasing temperatures, however there was a gradual erosion in *ee* (eg at reflux 90% yield, 29% *ee*). Cooling the reaction to 0 °C resulted in little change in *ee*, however the yield of cycloadduct **3** continued to fall (63% yield, 52% *ee*); below 0 °C *ee* was also eroded. Davies and co-workers have observed a significant effect of ester group size in asymmetric cyclopropanations using [Rh_2(*S*-DOSP)$_4$] **2** with ester-substituted vinyldiazomethanes (methyl esters giving the highest levels of enantioselectivity).[11] However, the Me and Bu^t-substituted α-diazo-β-ketoesters **1** (R = Me and Bu^t, n = 1)[7] gave similar *ees* (eg at room temperature 86% yield, 48% *ee* and 93% yield, 52% *ee* respectively). In order to probe the effect of rate of cycloaddition on *ee* we examined the α-diazo-β-ketoester **1** (R = Bu^t, n = 2)[7] which at room temperature gave cycloadduct **3** [R = Bu^t, n = 2, 77%, 48% *ee*, $[\alpha]^{20}_{D}$ -3.1 (*c* 1 in $CHCl_3$)].

To our knowledge these are the first examples of catalytic enantioselective tandem carbonyl ylide formation-cycloaddition and, more generally, indicate that metal-catalysed dipole formation followed by cycloaddition has the potential to be a powerful method for asymmetric synthesis. Further studies on the scope of this process (other substrates and catalysts) are in progress and will be reported in due course.

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