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Catalytic enantioselective intermolecular cycloadditions of a 2-diazo-3,6-diketoester-derived carbonyl ylide with alkyne and strained alkene dipolarophiles

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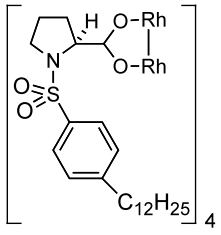
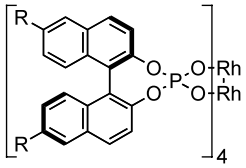
Abstract—Catalytic enantioselective tandem carbonyl ylide formation-cycloaddition reactions of *tert*-butyl 2-diazo-3,6-dioxoheptanoate **7** with alkyne and strained alkene dipolarophiles to afford the corresponding cycloadducts with up to 92% ee are described.

Compared with enantioselective Diels–Alder and hetero Diels–Alder processes, enantioselective 1,3-dipolar cycloadditions are relatively underdeveloped.[1] Nevertheless, the latter reaction class holds considerable potential for the asymmetric synthesis of heterocycles.[2] Studies by Padwa et al. established Rh(II)-catalysed tandem carbonyl ylide formation-1,3-dipolar cycloaddition of diazocarbonyl compounds as an excellent method for the synthesis of oxapolycycles.[3] In 1997, using this method, we reported the first examples of enantioselective carbonyl ylide cycloadditions: Unsaturated 2-diazo-3,6-diketoesters underwent intramolecular cycloaddition catalysed by Davies' prolinate catalyst $Rh_2[(S)\text{-DOSP}]_4$ **4**[4] with up to 52% ee (Fig. 1, Scheme 1).[5] Such cascade reactions are of interest because of the rapid generation of molecular complexity,[3] and the demands that they place upon a catalyst—which is required to efficiently decompose the diazo precursor *and* form a catalyst-associated ylide (e.g. **2**),[6] from which a highly (ideally) enantioenriched cycloadduct ensues.



$Rh_2[(S)\text{-DOSP}]_4$ **4**



R = H: $Rh_2[(R)\text{-BNP}]_4$ **5**
R = $C_{12}H_{25}$: $Rh_2[(R)\text{-DBBNP}]_4$ **6**

Figure 1.

Detailed catalyst studies using ester **1** eventually led to a hydrocarbon-soluble variant of Pirrung's phosphate catalyst $Rh_2[(R)\text{-BNP}]_4$ **5**:[7] $Rh_2[(R)\text{-DDBNP}]_4$ **6** (Fig. 1) was found to be capable of generating the intramolecular cycloadduct (+)-**3** (absolute configuration as shown in Scheme 1) in up to 90% ee.[8] In the corresponding intermolecular carbonyl ylide cycloaddition process, so far only DMAD as the dipolarophile has been shown capable of efficiently delivering cycloadducts in high ees: up to 92% ee was observed by Hashimoto and co-workers using 1-diazo-2,5-diketones, catalysed by α-phthalimido Rh(II) carboxylates.[9,10]

The above results, together with our recent studies using arylacetylene dipolarophiles with 1-aryl-1-diazo-2,5-diketones (up to 76% ee),[11] encouraged us to examine asymmetric intermolecular carbonyl ylide cycloadditions of a 2-diazo-3,6-diketoester with dipolarophiles which do not contain electron-withdrawing substituents on the reacting π-bond. Initial studies using *tert*-butyl 2-diazo-3,6-dioxoheptanoate **7**[12] with phenylacetylene (2 equiv.) and $Rh_2(OAc)_4$ or $Rh_2(tfa)_4$ as catalysts in CH_2Cl_2 or toluene at 25°C failed to

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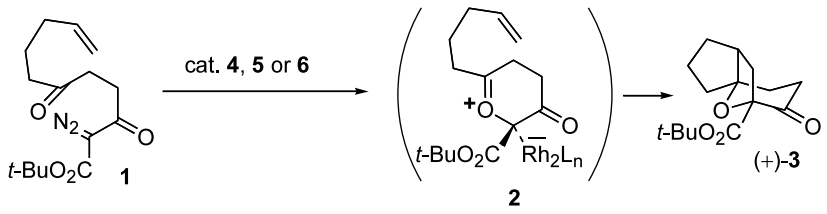
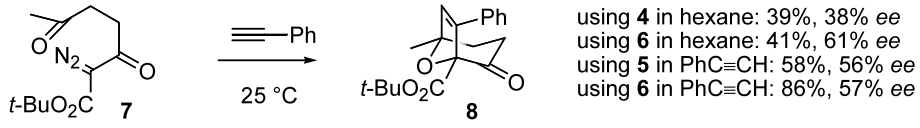


Scheme 1.

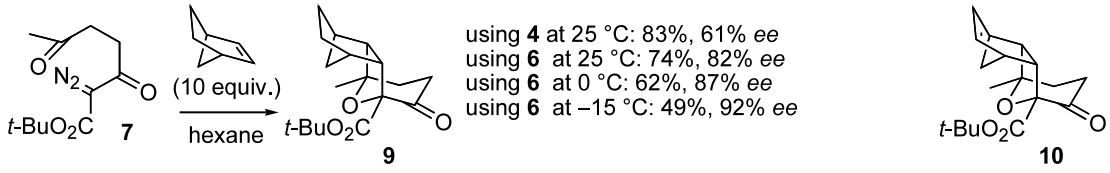
generate any of the desired cycloadduct. However, using 5 or 10 equiv. of phenylacetylene with $Rh_2(OAc)_4$ in CH_2Cl_2 gave cycloadduct **8**[13] in 7% and 18% yields, respectively (Scheme 2). Using fully hydrocarbon-soluble chiral catalysts Rh_2[(*S*)-DOSP]$_4$ **4** or Rh_2[(*R*)-DDBNP]$_4$ **6** with 10 equiv. of phenylacetylene in hexane led to improved yields of cycloadduct **8** (39% and 41%, respectively). Importantly, the ees obtained (38% and 61% using **4** and **6**, respectively)[14] gave the first indications that highly enantioselective intermolecular cycloadditions of dicarbonyl (doubly stabilised) carbonyl ylides were possible. Such ylides constitute one of the most widely used classes of carbonyl ylides,[3] due the typical stability, storage and ease of handling of the cycloaddition precursors which are easily prepared from 1,3-dicarbonyl compounds by diazo transfer. Our earlier studies had found that using phenylacetylene as both the solvent and dipolarophile was advantageous.[11] In the present case, using $Rh_2(OAc)_4$ and neat phenylacetylene ($\sim$170 equiv.) gave 59% yield of cycloadduct **8**. A similar yield (58%) and promising ee (56%) was obtained using Rh_2[(*R*)-BNP]$_4$ **5**. The yield could be improved (to 86%, 57% ee) using Rh_2[(*R*)-DDBNP]$_4$ **6**, and this improvement is likely to be a result of the fully-soluble nature of this phosphate catalyst under the reaction conditions.

Simple alkenes are normally unreactive in intermolecular carbonyl ylide cycloadditions.[15] Nevertheless, reaction of ester **7** with cyclopentene[16] was attempted. With 10 equiv. of cyclopentene using $Rh_2(OAc)_4$ in CH_2Cl_2 a 14% yield of cycloadduct could be obtained after 4 h; in neat cyclopentene 26% yield could be obtained after 7 h. However, using Rh_2[(*R*)-DDBNP]$_4$ **6** with cyclopentene (10 equiv.) gave no cycloadduct. There is more encouraging precedent for cycloaddition with norbornenyl systems.[16,17] Indeed, subjecting diazo substrate **7** to $Rh_2(OAc)_4$ catalysed decomposition in the presence of norbornene (1.5 equiv.) in hexane led to single cycloadduct **9** in 45% yield (structure determined by X-ray crystallographic analysis).[18] The selectivity obtained in this cycloaddition is consistent with other carbonyl ylide cycloadditions with norbornene.[16,17] With 10 equiv. of norbornene, under otherwise identical conditions, the reaction was complete in 30 min and the yield of cycloadduct **9** rose to 82%. Rh_2[(*S*)-DOSP]$_4$ **4** was found to deliver reasonable levels of asymmetric induction (83% yield of **9**, 61% ee).[19] Using chiral phosphate catalyst Rh_2[(*R*)-DDBNP]$_4$ **6** at room temperature gave significant asymmetric induction (74% yield, 82% ee) and on reducing the reaction temperature to 0°C and to −15°C, the ee rose to 87%[20] and 92%, respectively; the latter is the highest asymmetric induction observed so far with a dirhodium phosphate catalyst (Scheme 3).[8]

Norbornadiene (10 equiv.) also proved a viable dipolarophile with 2-diazo-3,6-diketoester **7** (78% of cycloadduct **10** using $Rh_2(OAc)_4$ in hexane at 25°C); Rh_2[(*S*)-DOSP]$_4$ **4** at 25°C and Rh_2[(*R*)-DDBNP]$_4$ **6** at 0°C gave **10** in 65% yield (79% ee) and 53% yield (83% ee), respectively.[21] The origin of the intriguing improvement in ee (from 61% to 79%) with Rh_2[(*S*)-DOSP]$_4$ **4** when using norbornadiene compared to norbornene is not obvious (in contrast, with Rh_2[(*R*)-DDBNP]$_4$ **6** the ee falls slightly: to 83% from 87%), but may relate to the faster reaction rate[6a] with norbornadiene (for **4**: 7 min, compared with 15 min for norbornene; for **6**: 15 min, compared with 35 min for norbornene). The reaction of 2-diazo-3,6-diketoester **7** with norbornadiene



Scheme 2.



Scheme 3.

using **4** provides the highest level of asymmetric induction seen with this catalyst in any carbonyl ylide cycloaddition thus far. This observation suggests that $Rh_2[(S)\text{-DOSP}]_4$ and structurally related catalysts, which have been used with considerable success in other enantioselective transformations of diazocarbonyl compounds,[4] continue to merit investigation in further studies of the current reaction class.

In summary, the first highly enantioselective intermolecular carbonyl ylide cycloadditions of a 2-diazo-3,6-diketoester substrate have been achieved. The highest levels of enantioselection recorded in the current study correlate well with those we have previously observed in intramolecular cycloadditions with structurally related dipoles,[8] and indicate that the presence of a tethered dipolarophile is not necessary for high asymmetric induction and that the enantioselectivity is not overly sensitive to the alkyl substituent at the ketone which forms the ylide. Further studies are currently underway to investigate the factors affecting the enantioselectivity of such cycloaddition processes.

Acknowledgements

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10. Enantioselective carbonyl ylide type cycloadditions of (aromatic) oxidopyryliums have also been reported: Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett*. **2000**, *41*, 5931–5935 (up to 93% ee using DMAD); Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc*. **2002**, *124*, 14836–14837 (up to 98% ee using an 3-acryloyl-2-oxazolidinone with a chiral Lewis acid–Rh catalyst combination).
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12. α-Diazo-β-ketoester **7** was prepared in an identical fashion to **1**,[8] from levulinic acid by homologation (58%) according to: Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 72–74, followed by diazo transfer (4-$AcNHC_6H_4SO_2N_3$, Et_3N, MeCN, 84%).
13. Cycloaddition regiochemistry (determined by NOE studies) is the same as that found[11] using arylacetylene dipolarophiles with 1-aryl-1-diazo-2,5-diketones.
14. Ees were determined by chiral HPLC (Daicel Chiralcel OD column with 90:10 heptane/EtOH eluant). Selected specific rotation value for **8** (61% ee, prepared using **6**): $[\alpha]_{24}^{D}$ −171.0 (*c* 1.0, $CHCl_3$). Hashimoto's optimized catalyst-solvent combination[9] was not examined in the present study, since it had previously been shown with **1** to generate only racemic cycloadduct **3**.[8]
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18. The X-ray crystal structure analysis of compound **9** will be reported elsewhere.
19. Ees were determined by chiral GC (CP Chirasil Dex-CD, 150°C isotherm, 1.0 ml min^{-1}, 2 mg ml^{-1}).
20. **Typical cycloaddition procedure:** To a stirred, degassed solution of *tert*-butyl 2-diazo-3,6-dioxoheptanoate **7** (50.0 mg, 0.21 mmol) and norbornene (196 mg, 2.1 mmol) in hexane (2.5 mL) at 0°C was added $Rh_2[(R)\text{-DDBNP}]_4$ **6** (6.1 mg, 0.0021 mmol). When the reaction was complete (35 min, TLC monitoring), the mixture was concentrated in vacuo. The residue was purified by flash silica gel chromatography (light petroleum–Et_2O 6:4; $R_f = 0.31$) to afford a white solid **9** (40 mg, 62%). $[\alpha]_D^{27}$ +45.6 (*c* 1.0, $CHCl_3$); m.p. 132–134°C; IR: (KBr)/cm^{-1} 2970 (C-Hst.), 2936 (C-Hst.), 2869 (C-Hst.), 1744 (C=Ost.), 1723 (C=Ost.), 1368, 1296, 1162, 1077, 842cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 2.66 (ddd, 1H, $^3J = 15.7$ Hz, $^3J = 12.1$ Hz, $^3J = 8.0$ Hz), 2.37 (app. s, 2H), 2.35–2.28 (m, 2H), 2.13–2.04 (m, 2H), 1.92 (ddd, 1H, $^3J = 13.1$ Hz, $^3J = 8.2$

Hz, $^4J=1.2$ Hz), 1.76 (dt, 1H, $^3J=10.1$ Hz, $^4J=1.8$ Hz), 1.54–1.48 (m, 2H), 1.52 (s, 9H), 1.37 (s, 3H), 1.22–1.14 (m, 2H), 1.00 (dt, 1H, $^3J=10.1$ Hz, $^4J=1.2$ Hz); ^{13}C NMR (100 MHz; $CDCl_3$): δ 201.1, 166.0, 90.9, 82.9, 82.3, 54.6, 53.7, 41.2, 39.2, 37.9, 34.2, 33.4, 28.9, 28.2, 28.1, 20.9; MS (CI-NH_3): m/z 324 ($M+NH_4^+$, 100%), 307 ($M+H^+$, 26%), 268 (30%); HRMS (ES, $[M+NH_4]^+$): calc. 324.2175, measured 324.2173.

21. Ees were determined by chiral GC (CP Chirasil Dex-CD, 155°C isotherm, 1.0 ml min^{-1}, 2 mg ml^{-1}). Selected specific rotation value for **10** (79% ee, prepared using **4**): $[\alpha]_D^{27}$ +67.1 (*c* 1.0, $CHCl_3$).