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Enantioselective intermolecular 1,3-dipolar cycloaddition via ester-derived carbonyl ylide formation catalyzed by chiral dirhodium(II) carboxylates

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Abstract

Enantioselective 1,3-dipolar cycloaddition of the ester-carbonyl ylides derived from methyl 2-(diazoacetyl)benzoate and 3-(diazoacetyl)-2-naphthoate with dipolarophiles has been effected with the aid of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], affording cycloadducts in up to 93% ee.

Copper or dirhodium(II) complex-catalyzed decomposition of α-diazo ketones tethered to a carbonyl group represents one of the most facile methods for the generation of cyclic carbonyl ylides.[1] Initially demonstrated by the Ibata group with copper catalysts,[2] the tandem carbonyl ylide formation and 1,3-dipolar cycloaddition methodology extensively advanced by the Padwa group with dirhodium(II) carboxylate catalysts is rapidly becoming recognized as a potentially powerful means for the construction of highly substituted oxygen-containing heterocycles.[3] Toward the development of a catalytic enantioselective version of this process,[4] we have recently found that tandem formation of the carbonyl ylides from α-diazo ketones **1** and 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) under the influence of Rh_2(*S*-BPTV)$_4$ incorporating *N*-benzene-fused phthaloyl-(*S*)-valine as a bridging ligand gives cycloadducts **3** in good yields and with up to 92% ee (Eq. (1)).[5] The high levels of enantioselection in the tandem reactions provide strong support for the intermediacy of the chiral rhodium(II)-associated carbonyl ylides **2** in the cycloaddition step.[6,7] Herein, we report that the original protocol can be extended to 1,3-dipolar cycloadditions via ester-derived carbonyl ylide formation from some selected α-diazo ketones,[8] in which Rh_2(*S*-PTTL)$_4$ has proven to be the catalyst of choice for achieving high enantioselectivities of up to 93% ee.

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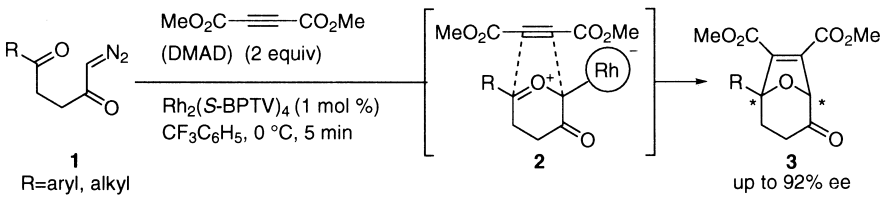
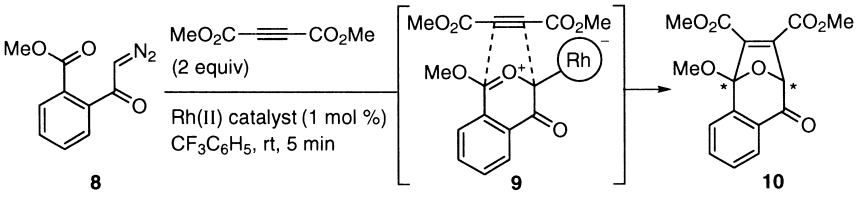


(1)

At the outset, we explored reactions of α-diazo ketones **4** and **6** tethered to an ester group in the presence of DMAD under the previously optimized conditions, using 1 mol% of Rh_2(*S*-BPTV)$_4$ in benzotrifluoride. In stark contrast to the results with α-diazo ketones **1**, it was found that the reaction of **4** afforded cycloadduct **5** of 14% ee, together with a complex mixture of products (Eq. (2)), with none of cycloadduct **7** being detected in the latter reaction (Eq. (3)). These disappointing results might be explained by the generally held view that the carbonyl group of an ester is much less reactive toward carbonyl ylide formation than that of a ketone.[1] In this respect, of particular interest is the pioneering work of Ibata and co-workers.[2] They demonstrated that the ester-derived carbonyl ylide from $Cu(acac)_2$-catalyzed decomposition of methyl 2-(diazoacetyl)benzoate (**8**) can be trapped by various dipolarophiles, usually in good yields. Patterned after the original work of Ibata, we thus examined Rh_2(*S*-BPTV)$_4$-catalyzed carbonyl ylide formation from **8** and subsequent cycloaddition with DMAD. Indeed, we were gratified to observe that the tandem reaction proceeded smoothly to provide cycloadduct **10**, $[\alpha]_D^{24}$ +169 (*c* 0.95; $CHCl_3$), in 72% yield with 62% ee (Table 1, entry 7).[9] At this stage, we evaluated the abilities of two classes of dirhodium(II) carboxylate catalysts incorporating *N*-phthaloyl- and *N*-benzene-fused phthaloyl amino acids shown in Fig. 1.[12] While a consistent sense of enantioselection was observed in all cases, percentage ee values were dependent on the catalyst. It is worthy of note that enantioselectivities were influenced more markedly by the alkyl group of amino acids than by the choice of *N*-phthaloyl- or *N*-benzene-fused phthaloyl groups. Of these catalysts, Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-BPTTL)$_4$, characterized by a bulky *tert*-butyl group, proved to be the catalysts of choice for displaying reasonable degrees of enantioselectivity (74% and 72% ee, Table 1, entries 4 and 8).[13,14]

Table 1
Chiral dirhodium(II) complex-catalyzed 1,3-dipolar cycloaddition of **8** with DMAD



Entry	Rh(II)	Yield[a] (%)	Ee[b] (%)	Entry	Rh(II)	Yield[a] (%)	Ee[b] (%)
1	Rh_2(*S*-PTPA)$_4$	67	44	5	Rh_2(*S*-BPTPA)$_4$	63	52
2	Rh_2(*S*-PTA)$_4$	69	35	6	Rh_2(*S*-BPTA)$_4$	68	34
3	Rh_2(*S*-PTV)$_4$	67	51	7	Rh_2(*S*-BPTV)$_4$	72	62
4	Rh_2(*S*-PTTL)$_4$	67	74	8	Rh_2(*S*-BPTTL)$_4$	68	72

[a]Isolated yield. [b]Determined by HPLC analysis using a Daicel Chiral OD; see ref 13.

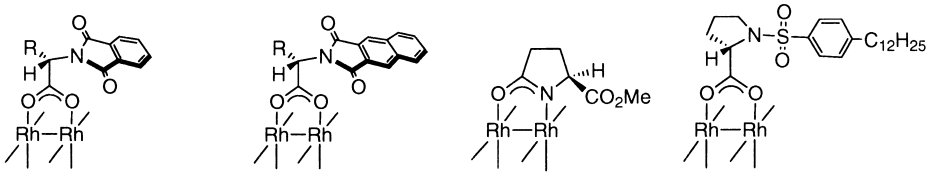
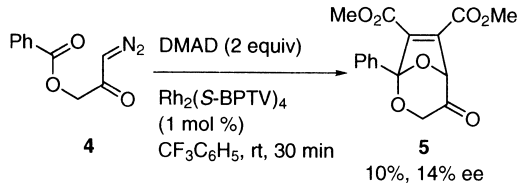
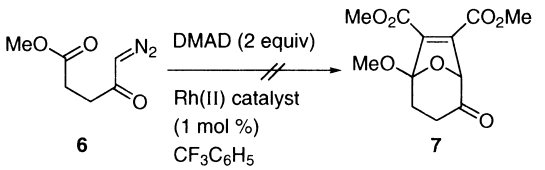


Figure 1.

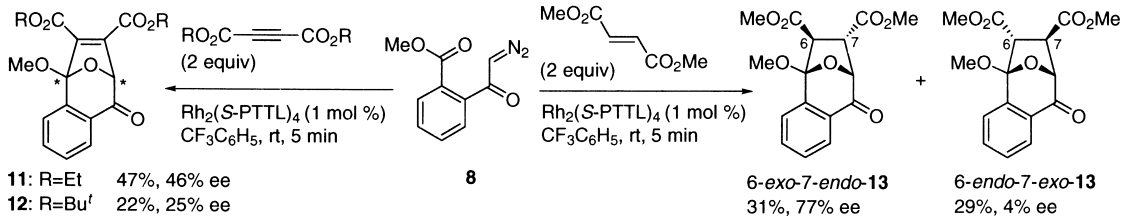


(2)



(3)

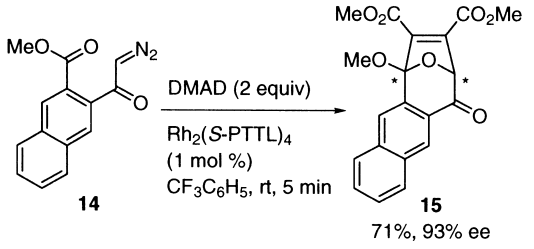
Using **8** as an ester-derived carbonyl ylide precursor and Rh_2(*S*-PTTL)$_4$ as a catalyst, we next explored the effect of dipolarophiles on the enantioselectivity (Scheme 1). To our surprise, switching the dipolarophile from DMAD to ethyl and *tert*-butyl esters of acetylenedicarboxylic acid markedly decreased product yields, as well as enantioselectivities (46% and 25% ee).[17] The reaction with dimethyl fumarate gave cycloadducts **13**[2b] in 60% yield as a 1:1 mixture of 6-*exo*-7-*endo*- and 6-*endo*-7-*exo* isomers, with 77% and 4% ee, respectively.[17] On the other hand, the use of dimethyl maleate or maleic anhydride resulted in a complex mixture of products. While the mechanistic profile is not clear, these results clearly indicate that the steric nature of dipolarophiles profoundly influences the enantioselectivity as well as the cycloaddition efficiency.[18]



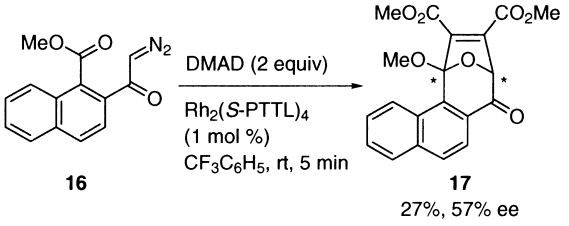
Scheme 1.

Finally, we extended the present protocol to the closely related α-diazo ketones, methyl 3-(diazoacetyl)-2-naphthoate (**14**) and methyl 2-(diazoacetyl)-1-naphthoate (**16**) (Eqs. (4) and (5)). Gratifyingly, the reaction of **14** with DMAD in the presence of 1 mol% of Rh_2(*S*-PTTL)$_4$ proceeded quite smoothly to produce cycloadduct **15** in 71% yield with 93% ee,[17,19] whereas that

of **16** under similar conditions gave cycloadduct **17** in 27% yield with 57% ee.[17] These results suggest that the shape of the aromatic backbones connected with the two functionalities in a 1,2 fashion is one of the most critical factors for success in this methodology.



(4)



(5)

In summary, we have succeeded in catalytic, enantioselective tandem cyclization–intermolecular cycloaddition of α-diazo ketones tethered to an ester group by the use of Rh_2(*S*-PTTL)$_4$, albeit with limited substrates and dipolarophiles. High levels of enantioselectivity (up to 93% ee) with this system have again demonstrated that chiral dirhodium(II) catalysts are intimately bound to carbonyl ylides during the cycloaddition process.

References

1. (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–269. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp. 355–432.
2. (a) Ibata, T.; Jitsuhiro, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3582–3585. (b) Ibata, T.; Jitsuhiro, K.; Tsubokura, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 240–244.
3. Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22–28.
4. Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98,* 911–935.
5. Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417–1418.
6. More recently, Hodgson and co-workers have reported a dramatic enhancement of up to 90% ee in tandem carbonyl ylide formation and intramolecular 1,3-dipolar cycloaddition of unsaturated α-diazo β-keto ester by using 0.5 mol% of dirhodium(II) tetrakis[(*R*)-6,6′-didodecyl-1,1′-binaphthyl-2,2′-diyl phosphate]: Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun.* **1999**, 2185–2186.
7. For other examples of catalyst-dependent regio- and diastereocontrol in this class of reactions, see: (a) Padwa, A.; Austin, D. J.; Hornbuckle, S. F. *J. Org. Chem.* **1996**, *61*, 63–72. (b) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210–7215.
8. Suga and Ibata recently reported that Rh_2(5*S*-MEPY)$_4$-catalyzed decomposition of methyl 2-(diazoacetyl)benzoate in the presence of *N*-phenylmaleimide afforded 1,3-dipolar cycloadduct in high *exo*-selectivity, albeit in low enantioselectivities (*endo*: 20% ee; *exo*: 5% ee): Suga, H.; Ishida, H.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 3165–3166.

9. Ibata and co-workers reported that replacement of the ester functionality in **8** with acyl groups such as benzoyl or acetyl led to very poor yields of cycloadducts with DMAD.[10] Padwa and co-workers reported that tandem ester-derived carbonyl ylide formation and intramolecular 1,3-dipolar cycloaddition gave none of the cycloadducts in those systems where an ester and a diazo ketone moiety were held apart by cyclic aliphatic backbones, whereas reactions of the corresponding keto analogues proceeded smoothly.[11] While the discrepancy between the diazo keto ester's reactivity and that of the diazo dione analogue remains to be clarified, these results, together with our results with **4** and **6**, clearly indicate that aromatic backbones are responsible for the preparation and subsequent cycloaddition of ester-derived carbonyl ylides, while an aliphatic tether is beneficial in cases of keto-derived carbonyl ylides. In the event, we found that Rh_2(*S*-BPTV)$_4$-catalyzed decomposition of 2-diazo-2′-benzoylacetophenone in the presence of DMAD afforded 1,3-dipolar cycloadduct in 11% yield and 15% ee, together with a complex mixture of products.
10. Ibata, T.; Ueda, K.; Takebayashi, M. *Sci. Rep. Coll. Gen. Educ. Osaka Univ*. **1976**, *25*, 19–22.
11. Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem*. **1989**, *54*, 817–824.
12. Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775–1777 and references cited therein.
13. A representative experimental procedure is illustrated as follows. A solution of diazo ketone **8** (50.0 mg, 0.245 mmol) in benzotrifluoride (1 ml) was added in one portion to a stirred solution of DMAD (71 mg, 0.49 mmol) and bis(ethyl acetate) adduct of Rh_2(*S*-PTTL)$_4$ (3.5 mg, 1 mol%) in benzotrifluoride (2 ml) at 23°C. After 5 min of stirring at this temperature, the resultant greenish solution was concentrated *in vacuo* and purified by column chromatography (silica gel, 9:1 hexane:ethyl acetate) to give cycloadduct **10** (49.7 mg, 67%) as a colorless oil. The enantiomeric excess was determined to be 74% by HPLC (Daicel Chiralcel OD). Absolute configuration of the product was not determined.
14. Enantioselectivities observed with the well-established dirhodium(II) catalysts, Rh_2(5*S*-MEPY)$_4$[15] and Rh_2(*S*-DOSP)$_4$,[16] were 1% and 12% ee, respectively, suggesting the unique ability of our dirhodium(II) catalysts.
15. Doyle, M. P. *Aldrichim. Acta* **1996**, *29*, 3–11.
16. Davies, H. M. L. *Aldrichim. Acta* **1997**, *30*, 107–114.
17. The enantiomeric excess was determined by chiral HPLC. Absolute configuration of the product was not determined.
18. The reaction of **8** with *N*-phenylmaleimide afforded cycloadducts in 60% yield (*endo*: 13% ee; *exo*: 3% ee).
19. A substantial drop in product yield as well as lower ee was observed with Rh_2(*S*-BPTTL)$_4$ (36% yield, 82% ee).