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The Scope of Catalytic Enantioselective Tandem Carbonyl Ylide Formation−Intramolecular [3 + 2] Cycloadditions

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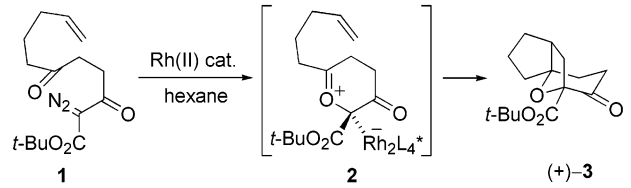
Catalytic enantioselective tandem carbonyl ylide formation−intramolecular 1,3-dipolar cycloaddition reactions of 2-diazo-3,6-diketoesters show promising scope in terms of asymmetric induction as the tethered alkene/alkyne dipolarophile component is varied. Cycloadditions were found to occur in moderate to very good yields, with a difference in ee exhibited by the electronically different 2-diazo-3,6-diketoesters **1**, **25** and **33**, **34**. Values for ee of up to 90% for alkene dipolarophiles and up to 86% for alkyne dipolarophiles were obtained.

Catalytic asymmetric synthesis is widely recognized as an attractive and powerful concept to access enantioenriched materials.[1] The utility of developing this concept in the context of tandem carbonyl ylide formation−1,3-dipolar cycloaddition reaction sequences from diazo substrates (Scheme 1, for example) lies in the rapid generation of molecular complexity being coupled with simultaneous control over the generation of absolute stereochemistry.[2] Such cascade processes, catalyzed in the racemic sense using achiral copper or rhodium complexes, were developed by Ibata and, particularly, Padwa as a method to concisely construct oxapolycycles containing an embedded reduced furan ring.[3] Since the late 1960s and with increasing intensity from approximately 1990 onward, chiral catalysts have been investigated with considerable success for generating enantioenriched products in many important transformations of diazo compounds, such as cyclopropanations and, more recently, C−H insertions.[3b] In contrast, catalytic enantioselective rearrangements and cycloadditions involving ylides from diazo compounds have been investigated only sporadically and with comparatively little success until the past few years.[4] In part, this reflects the challenging

SCHEME 1. Tandem Catalyzed Carbonyl Ylide Formation−Cycloaddition



using **4** at 25 °C : 77% yield, 52% ee

using **7** at 25 °C : 76% yield, 81% ee
at 0 °C : 81% yield, 88% ee
at −15 °C : 66% yield, 90% ee

role required of the chiral catalyst in which, for good enantioselectivity in the reaction shown in Scheme 1, for example, it must smoothly transform the diazo substrate **1** into a catalyst-associated ylide **2** and then efficiently mediate facial selectivity in the cycloaddition event [making the reasonable assumption that cycloaddition via the achiral (catalyst-free) carbonyl ylide would lead to a racemic cycloadduct]. Following our first demonstration in 1997[5] of enantioselective carbonyl ylide cycloaddition in up to 52% ee with 2-diazo-3,6-diketoesters such as **1** utilizing Davies' prolinate catalyst Rh_2(*S*-DOSP)$_4$ **4**,[6] Hashimoto and co-workers subsequently reported high levels of asymmetric induction (up to 92% ee) with catalyst Rh_2(*S*-BPTV)$_4$ **5** in intermolecular cycloadditions using diazodiones with DMAD as the dipolarophile.[7] Although application of Hashimoto's optimized catalyst−solvent combination (Rh_2(*S*-BPTV)$_4$ **5**, $PhCF_3$ as solvent)

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(2) (a) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002. (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002.

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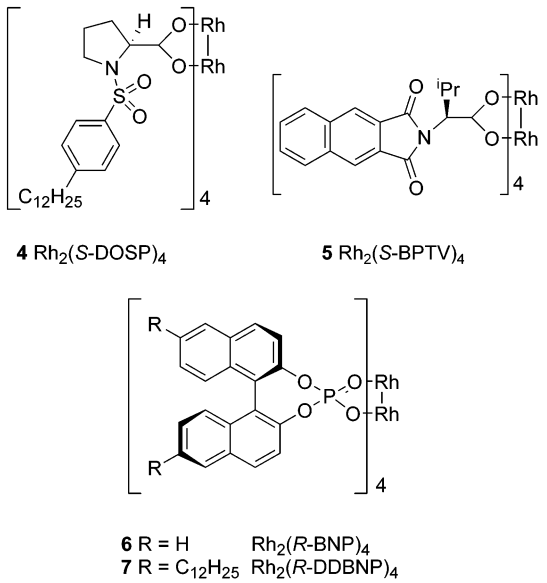

4 Rh_2(*S*-DOSP)$_4$ **5** Rh_2(*S*-BPTV)$_4$

6 R = H Rh_2(*R*-BNP)$_4$
7 R = $C_{12}H_{25}$ Rh_2(*R*-DDBNP)$_4$

FIGURE 1. Chiral rhodium catalysts.

to ester **1** at 25 °C resulted in only essentially racemic cycloadduct **3** (90% yield, 1% ee), further catalyst studies using ester **1** eventually led us to a hydrocarbon-soluble variant of Pirrung's phosphate catalyst Rh_2(*R*-BNP)$_4$ **6**:[8] Rh_2(*R*-DDBNP)$_4$ **7** was found capable of generating intramolecular cycloadduct (+)-**3** (absolute configuration as shown in Scheme 1) in up to 90% ee.[9] To probe electronic effects of the dipole on asymmetric induction, enantioselective cycloadditions of diazoketone-derived aryl-substituted carbonyl ylides have been studied.[10] Using Rh_2(*R*-DDBNP)$_4$ **7** we have also recently reported significant enantiomeric excesses (up to 92% ee) in intermolecular cycloadditions with strained alkenes (such as norbornene) and 2-diazo-3,6-diketoesters similar to **1**, but lacking side chain unsaturation.[11] Enantioselective carbonyl ylide type cycloadditions of (aromatic) oxidopyryliums have also been studied. Although only low ee values have been observed so far in intramolecular cycloadditions of oxidopyryliums (up to 19% ee),[12] for the intermolecular process up to 93% ee using DMAD and catalyst **5** has been recorded[13] and up to 98% ee has been reported using a 3-acryloyl-2-oxazolidinone dipolarophile with a chiral Lewis acid−Rh catalyst combination.[14]

The principal focus of the work described herein was to develop an appreciation of the effect on ee of changing the dipolarophile in intramolecular carbonyl ylide cycloadditions, using substrates related to **1** with catalysts **4** and **7**. With respect to the dipolarophile in the enantioselective intramolecular process, only studies with a simple, unsubstituted terminal alkene have been reported in detail thus far (Scheme 1).[9] Thus, the current study would give an idea of the scope of this methodology for asymmetric synthesis and hopefully provide some insight into the nature of the factors influencing asymmetric induction. To achieve this aim, it was considered important to study substrates that allowed examination of variations in the length of the tether to the dipolarophile, as well as its level and pattern of alkyl substitution and degree of unsaturation (alkene, alkyne).[15] A strategy is also demonstrated that permits greater flexibility in the nature of the dipolarophile substituent, especially for the introduction of polar functionalities.

The original synthesis of **1**[9] was adapted for the construction of cycloaddition substrates **25**−**34** (Scheme 2). In this strategy, unsaturated 4-ketoacids **8**−**14** were chemoselectively homologated by activation as the acyl imidazolides and reaction with the magnesium salt of mono *tert*-butyl malonate.[16] This chemistry led to 3,6-diketoester functionality from which the desired cycloaddition substrates **25**−**34** arose following diazo transfer at the doubly activated methylene group. The 4-ketoacids **8**−**14** were accessed via lithiation of 2,3-dihydrofuran and alkylation with the appropriate alkenyl iodide or (TMS-protected) alkyne, followed by direct oxidation of the crude alkylated dihydrofuran using Jones' reagent.[17] For the cases of the TMS-protected alkynes, protodesilylation conveniently occurred concomitantly during oxidation, leading to the terminal alkynes **11** and **13**. (*E*)-Alkene **25** and (*Z*)-alkene **26** were synthesized to study if the asymmetric cycloaddition process exhibited stereospecificity. Whereas (*E*)-alkene **25** originated from commercially available (*E*)-4-hexen-1-ol (*E*:*Z*, 98:2 by GC), Lindlar reduction of the acetylenic diketoester derived from 4-ketoacid **12** gave, after diazo transfer, (*Z*)-alkene **26** (*Z*:*E*, 90:10).

To increase flexibility in the nature of the dipolarophile in intramolecular cycloaddition substrates, we examined a cross-metathesis strategy.[18] With methyl acrylate and the 3,6-diketoesters **49** and **17** (precursors to cycloaddition substrates **1** and **27**), metathesis reactions using the second-generation ruthenium catalyst $(PCy_3)(L)Ru{=}CHPhCl_2$ (L = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) pleasingly produced unsaturated diketodiesters **23** and **24** in excellent yields (96% and 87%, respectively) and with good control over alkene stereochemistry (*E*:*Z*, 93:3) (Scheme 3). Furthermore, subsequent diazo transfer proceeded smoothly in the presence of the α,β-unsaturated ester functionality to deliver cycloaddition precursors **33** and **34** in good yields (84% and 82%, respectively).

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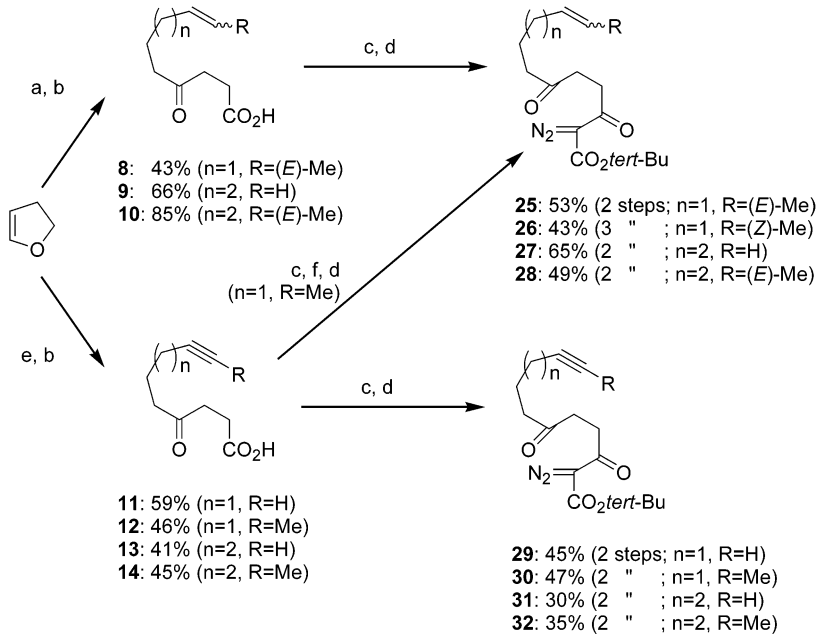
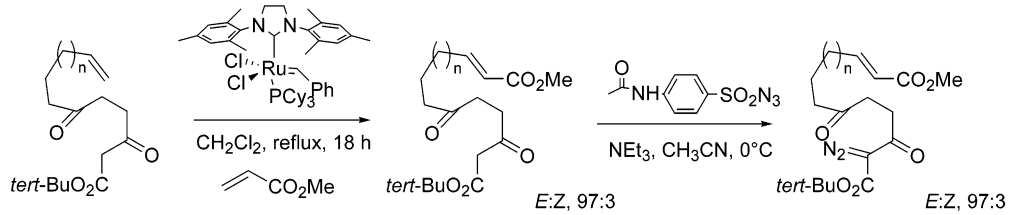
SCHEME 2. Synthesis of 2-Diazo-3,6-diketoester Substrates[a]



[a] (a) *t*-BuLi (1.2 equiv), RCH═$CH_2CH_2(CH_2)_nCH_2I$ (1 equiv), THF, −60 to 25 °C, 18 h; (b) Jones' reagent (3 equiv), THF, 0 °C, 18 h; (c) carbonyldiimidazole (1.2 equiv), THF, 0 °C, then $Mg(O_2CCH_2CO_2t\text{-}Bu)_2$ (1.1 equiv), THF, 25 °C, 18 h, then H_3O^+; (d) 4-$(NHAc)C_6H_4SO_2N_3$ (1.1 equiv), Et_3N (1.1 equiv), MeCN, 0 °C, 5 h; (e) *t*-BuLi (1.2 equiv), RC≡$CHCH_2(CH_2)_nCH_2I$ (1 equiv), THF, −60 to 25 °C, 18 h; (f) H_2 (1 atm), Lindlar's catalyst, quinoline, petroleum ether, 25 °C, 5.5 h.

SCHEME 3. Synthesis of 33 and 34 by Catalyzed Cross-Metathesis and Diazo Transfer Reactions



49 n = 1
17 n = 2

23 n = 1
24 n = 2

33 n = 1
34 n = 2

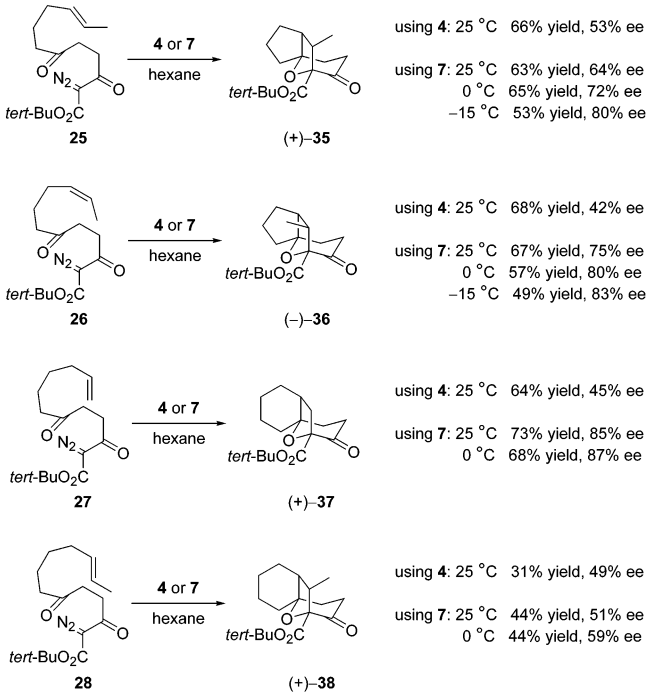
The viability of the diazo substrates to undergo the desired ylide formation−cycloaddition process was established by treatment with rhodium(II) acetate in CH_2Cl_2 at 25 °C (40−80% yields of cycloadducts); these racemic cycloadducts were also used for establishing enantiomeric purity determination assays by GC.[19] Both Rh_2(*S*-DOSP)$_4$ **4** and Rh_2(*R*-DDBNP)$_4$ **7** were then examined with the cycloaddition substrates in hexane. Results in CH_2Cl_2 are described in Supporting Information; as previously found with **1**,[9] the ee values were uniformly lower than those in hexane. Cycloaddition substrates (*E*)- and (*Z*)-alkenes **25** and **26**, differing only in alkene stereochemistry, successfully underwent cycloaddition to give structurally different (epimeric) cycloadducts **35** and **36**, respectively (Scheme 4). The absolute configurations of the predominant cycloadduct enantiomers are tentatively assigned as those shown, by analogy with cycloadduct (+)-**3** of known absolute configuration.[9]

Although both cycloaddition substrates **25** and **26** contained minor amounts of the other alkene stereoisomer (as discussed above), there was no increase in the relative proportion of (chromatographically separable) cycloadduct that could be attributed to the minor isomer in each case. nOe experiments with cycloadduct **36** established that the *cis* methyl group in the precursor alkene **26** remained *cis* to the side chain that evolved into the cyclopentyl group.[20] Further evidence for the stereochemistry of cycloadduct **36** is found in the fact that hydrogenation of **40** (vide infra) leads to **36**, and not **35**. Cycloadduct **35** is therefore unambiguously assigned as the methyl epimer of **36**, and the stereochemistry of cycloadduct **38** arising from *trans* alkene **28** is assigned by analogy to that of **35**. We conclude from the reactions of alkenes **25** and **26** that the intramolecular addition to simple nonpolarized alkenes of the putative catalyst complexed carbonyl ylide (cf **2**, Scheme 1) is stereospecific. As a corollary we note that these reactions illustrate for the first time the synthetically important ability to control up to four stereocenters in such an enantioselective intramolecular cycloaddition process. We were also pleased to observe that ee values (up to 80% and 83%

(19) See Supporting Information for details.

(20) Key nOe's for cycloadduct **36** are shown in Supporting Information.

SCHEME 4. Cycloaddition Reactions with Alkene Diazo Substrates 25−28



for **35** and **36**, respectively) were only slightly lower than the best obtained with the unsubstituted alkene substrate **1**. The reaction's ability to tolerate any structural variation in the dipolarophile while maintaining good ee values was by no means assured, since Hashimoto had observed a significant erosion in ee (and yield) for one (oxidopyrylium) substrate as the dipolarophile was even varied from DMAD (74% ee) to the corresponding diethyl ester (46% ee); 25% ee was observed with the di(*tert*-butyl) ester.[13]

It is also interesting to note that for the cycloadditions of (*E*)- and (*Z*)-alkenes **25** and **26**, under a given set of reaction conditions, there were small but significant differences in ee values between the two geometric isomers, but the effect was opposite for the carboxylate and phosphate catalysts. That is, Rh_2(*S*-DOSP)$_4$ **4** gave slightly higher ee with (*E*)-**25** compared to (*Z*)-**26** (at 25 °C, 53% ee, versus 42% ee, respectively), whereas Rh_2(*R*-DDBNP)$_4$ **7** gave slightly better asymmetric induction with (*Z*)-**26** (for example, at 25 °C, 75% ee using (*Z*)-**26**, versus 64% ee using (*E*)-**25**.

Padwa originally established that the rate of intramolecular cycloaddition of a carbonyl ylide containing a hexenyl tether was slower than that for an ylide containing a tethered pentenyl dipolarophile (cf. that derived from **1** (with CO_2t-Bu = H)), as the former (but not the latter) dipole could be trapped intermolecularly if the reaction was run in the presence of DMAD.[21] It was therefore pleasing to observe that cycloaddition of diazo diketoester **27**, bearing a hexenyl tether, occurred in similar levels of ee compared to the basic pentenyl-substituted substrate **1** (up to 87% ee using Rh_2(*R*-DDBNP)$_4$ **7** at 0 °C with **27**; 88% ee was observed with **1** under these conditions), despite the former's presumed slower rate of cycloaddition. A slower rate of cycloaddition could potentially affect the level of asymmetric induction if catalyst dissociation from the putative catalyst-associated ylide (eg **2**, Scheme 1) occurred to give (some of) the achiral catalyst-free carbonyl ylide prior to the cycloaddition step.[4a] Intriguingly, a more substituted alkene appeared more sensitive to variation in tether length with respect to ee, since for the (*E*)-alkene **28** there was a noticeable reduction in ee compared with (*E*)-alkene **25** (e.g., using Rh_2(*R*-DDBNP)$_4$ **7** at 0 °C, 59% ee compared to 72% ee, respectively).

Cycloadditions with the substrates bearing an ester conjugated to the alkene dipolarophile proceeded in good yields, whichever catalyst was used (Scheme 5). However, the ee values obtained were much lower than those observed with unpolarized alkene dipolarophiles. We did not study Hashimoto's optimized catalyst−solvent combination (Rh_2(*S*-BPTV)$_4$ **5** in $PhCF_3$)[7] with the unpolarized systems above, since that combination had previously been shown with **1** to generate only racemic cycloadduct **3**.[9] However, it was of interest to determine if the presence of an electron-deficient dipolarophile altered the outcome. In the event, although cycloadditions proceeded efficiently (93% and 95% for **43** and **44**, respectively), ee values were low (18% and 17%, respectively). Our previous studies of related carbonyl ylide cycloadditions indicated that a complex blend of electronic effects from the dipole and dipolarophile, together with the nature of the catalyst, contribute to the origin of asymmetric induction.[10] However, the current results with catalysts **4** and **7** (Schemes 4 and 5) follow a trend that when the dipole and dipolarophile have similar electronic characteristics (both electron-deficient for **33** and **34**) the ee is lower than when they oppose (electron-deficient dipole and simple nonpolarized alkene dipolarophile).

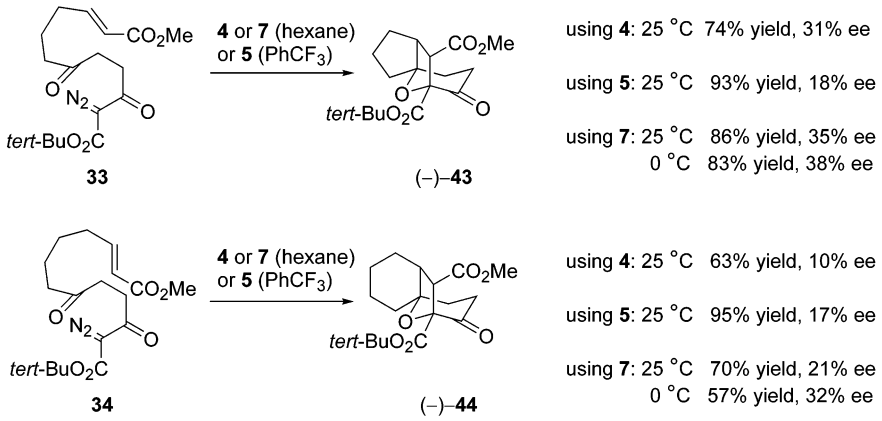
With the aim of generating enantioenriched cycloadducts that retained useful functionality for additional synthetic manipulations and also to further probe the effect on ee with respect to dipolarophile, we next examined cycloaddition substrates bearing tethered acetylenic functionality (Scheme 6).[22]

Given the earlier comments concerning substrate generality, it was pleasing to find that the results with intramolecular acetylenic dipolarophiles generally paralleled those previously found with tethered alkenes. Also, hydrogenation of (+)-**39** ($[\alpha]^{25}_D$ +293.5, c = 1.0 in $CHCl_3$) and (+)-**40** ($[\alpha]^{27}_D$ +266.2, c = 1.0 in $CHCl_3$) gave (+)-**3** (95% yield, $[\alpha]^{27}_D$ +9.9, c = 1.0 in $CHCl_3$) and (−)-**36** ($[\alpha]^{27}_D$ −15.3, c = 1.0 in $CHCl_3$), respectively; this establishes that the same sense of asymmetric induction is observed with both alkene and alkyne dipolarophiles. For identical reaction conditions similar ee values were often observed for alkene and alkyne systems in which the tether length (3 or 4 methylene groups) and substitution pattern (terminal or internal unsaturation) were the same. Typically, the alkyne systems gave cycloadduct ee values a little less (usually within 10%) than the analogous alkene systems. One noteworthy exception is found in comparing the 4 methylene-tethered internally unsaturated systems **28** and **32**, where the acetylenic system

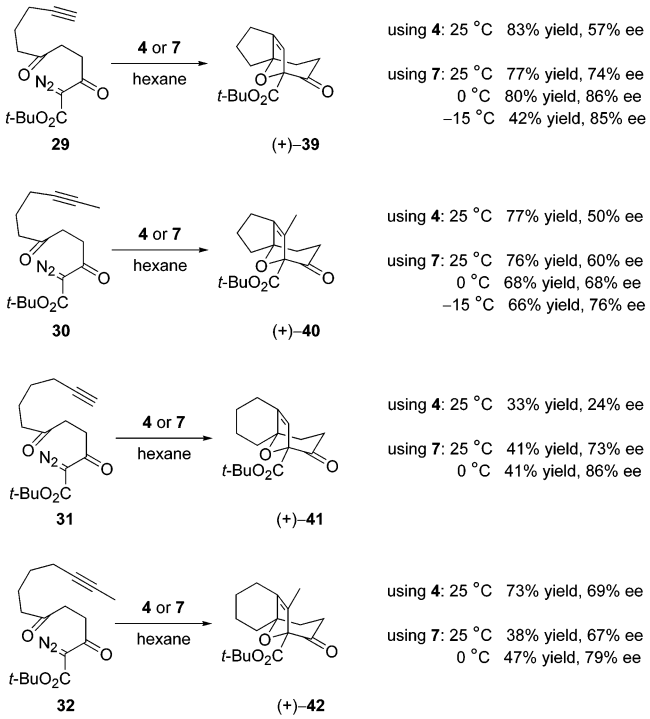
(21) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Zhang, Z. J. *J. Org. Chem.* **1992**, *57*, 5747−5757.

(22) For a recent example, see: Graening, T.; Friedrichsen, W.; Lex, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1524−1526.

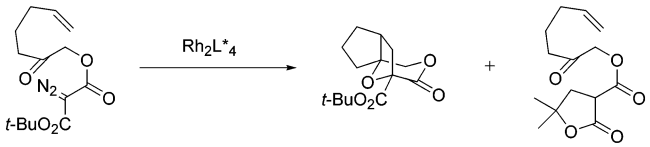
SCHEME 5. Cycloaddition Reactions with Alkene Diazo Substrates 33 and 34



SCHEME 6. Cycloaddition Reactions with Alkyne Diazo Substrates 29−32



SCHEME 7. Cycloaddition Reactions with Mixed Diazomalonate 47



	47	**(+)–48a**	**48b**
using **4**:	CH_2Cl_2, reflux, 2 h	54% yield, 1% ee	21% yield
	hexane, reflux, 3 h	41% yield, 5% ee	6% yield
	benzene, reflux, 1 h	57% yield, 3% ee	–
using **5**:	$PhCF_3$, 25 °C, 1.5 h	39% yield, 0% ee	20% yield
using **6**:	CH_2Cl_2, 25 °C, 2 h	27% yield, 14% ee	39% yield
	CH_2Cl_2, reflux, 2 h	24% yield, 13% ee	25% yield
	hexane, reflux, 3 h	27% yield, 18% ee	–
	benzene, reflux, 0.5 h	47% yield, 11% ee	9% yield
using **7**:	hexane, 25 °C, 2 h	12% yield, 43% ee	–

32 generated cycloadduct **42** with ee values some 20% higher than those found for the corresponding alkene derived cycloadduct **38**. In particular, using substrate **32**, Rh_2(*S*-DOSP)$_4$ **4** reproducibly delivered the highest level of asymmetric induction (69% ee) seen with this catalyst in any intramolecular carbonyl ylide cycloaddition thus far and in good yield (73%). This latter result may also be compared both with the corresponding 3 methylene-tethered internally substituted alkyne **34**, for which with Rh_2(*S*-DOSP)$_4$ **4** generated the cycloadduct **40** in only 39% ee (74% yield), and with the 4 methylene-tethered terminal alkyne **31** where the cycloadduct **41** was only generated in 24% ee. These latter results highlight once again that a complex interplay of factors determine asymmetric induction in these cycloadditions.

With the aim of exploring further the scope of enantioselective tandem carbonyl ylide formation−intramolecular cycloaddition chemistry, the mixed diazomalonate **47** was selected for examination (Scheme 7); comparison of this substrate with **1** would allow an assessment of the effect of the oxygen for methylene replacement on cycloaddition efficiency and asymmetric induction. Padwa had earlier reported that the corresponding ethyl ester (**47**, *t*-Bu = Et) was a viable substrate for the cycloaddition chemistry, catalyzed by rhodium acetate.[23] However, the *tert*-butyl ester was studied in the present work, since our previous results indicated that larger ester substituents led to the best ee values, at least with phosphate catalysts such as **6** and **7**.[9]

In the event, diazomalonate **47** was found to be somewhat less reactive in the cycloaddition chemistry than the *β*-ketoesters studied earlier, with **47** requiring temperatures above ambient to achieve complete cycloaddition in a reasonable time scale (∼3 h). Attenuated reactivity of diazomalonates compared with α-diazo-*β*-ketoesters is often observed in diazo chemistry.[3b] While reaction under rhodium acetate catalysis provided tricyclic lactone cycloadduct **48a** in satisfactory yields (benzene, reflux, 15 min, 74%; CH_2Cl_2, reflux, 15 min, 46%), reaction under asymmetric catalysis with Rh_2(*S*-DOSP)$_4$ and with the phosphate catalysts generally provided cycloadduct **48a** in only modest yields (Scheme 7). In most cases the lactone **48b**, arising from simple intramolecular C−H insertion[3b] was also isolated as a

(23) Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L. *J. Org. Chem.* **1993**, *58*, 4646−4655.

byproduct. As related byproducts were not observed in our earlier studies, this suggests that carbonyl ylide formation (and/or cycloaddition) is slower from the diazomalonate **47** compared with the β-ketoester substrates. Moreover, the ee values for tricyclic lactone cycloadduct **48** were significantly lower than those obtained with the original cycloaddition substrate **1**, with only the Rh_2(*R*-DDBNP)$_4$ catalyst providing any encouraging signs of asymmetric induction, albeit in very low chemical yield.

Clearly, the oxygen for methylene replacement resulted in severe erosion of both cycloaddition efficiency and asymmetric induction. The lower cycloaddition efficiency may be due to the propensity for esters to exist in the *s-trans* conformation, together with the inductive effect of the newly introduced ester group reducing the propensity of the ketone to participate in carbonyl ylide formation. Although both of these factors are also operative in Padwa's successful corresponding ethyl ester system,[21] in the current case a competing C−H insertion (with the *tert*-butyl ester) serves to reduce yields. If one of the major factors determining asymmetric induction in these cycloadditions is insertion selectivity of the tethered ketone into the *re* or *si* face of the putative intermediate chiral metallocarbene,[4a] then the origin of the reduced asymmetric induction when using **47** could be that this insertion is (more) reversible in the case of **47**, since the derived metallocarbene is less electrophilic and the ketonic oxygen lone pair less nucleophilic than that from **1**. Thus, reversibility in the formation of the catalyst-complexed ylide (cf. **2**) could compromise asymmetric induction.

It is important to note that the results described with Rh_2(*S*-DOSP)$_4$ **4** above related to material prepared according to the procedure of Davies[6] but using isomerically pure dodecyl substituents. The commercially available Rh_2(*S*-DOSP)$_4$ catalyst (which contains a mixture of undecyl to tridecyl substituents) gave essentially identical yields for all the alkyne substrates **29**−**32**, and ee values were also unaffected for the terminal alkynes **29** and **31** (all reactions with Rh_2(*S*-DOSP)$_4$ **4** have been carried out at 25 °C). Intriguingly however, the methyl-substituted alkynes **30** and **32** reproduceably delivered lower ee values when using the commercial catalyst: 38−39% ee (2 runs) for **40** compared with 50% ee, and 57−59% ee (2 runs) for **42** compared with 68−71% ee (3 runs).

In summary, enantioselective intramolecular 1,3-dipolar cycloadditions of unsaturated 2-diazo-3,6-diketoester-derived carbonyl ylides show promising scope in terms of asymmetric induction as the tethered dipolarophile component is varied; a structurally related diazomalonate **47** is less successful. The stereospecificity of the process, the creation of up to four stereocenters, a potentially versatile cross-metathesis strategy for substrate preparation, and enantioselective intramolecular cycloadditions with alkynes (in up to 86% ee) have all been demonstrated for the first time.

Experimental Section

General Methods. All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were oven-dried and allowed to cool in a desiccator over self-indicating silica gel prior to use. All solvents were distilled before use. Ethers were distilled from sodium/benzophenone ketyl, and (halogenated) hydrocarbons and MeCN from CaH_2. "Petrol" refers to the fraction of light petroleum ether boiling between 30 and 40 °C. $Rh_2(OAc)_4$ and Rh_2(*S*-DOSP)$_4$ were purchased commercially. Synthesized Rh_2(*S*-DOSP)$_4$ was prepared according to Davies' procedure, using pure 4-dodecylbenzenesulfonyl chloride.[6] Hashimoto's procedure was followed for the preparation of Rh_2(*S*-BPTV)$_4$.[7,13] Rh_2(*R*-BNP)$_4$ was prepared according to Pirrung's procedure.[8] Rh_2(*R*-DDBNP)$_4$ was prepared as we previously reported.[9b] Reactions were monitored by TLC using commercially available aluminum plates precoated with silica (0.25 mm, Merck 60 F_{254}), which were developed using standard visualizing techniques: UV fluorescence (254 nm) and/or potassium permanganate or vanillin solution, heating. Flash chromatography was performed on Kieselgel 60 (40−63 μm).

Representative Synthesis of a 2-Diazo-3,6-diketoester (25). (*E*)-6-Iodo-2-hexene.[24] A solution of (*E*)-4-hexen-1-ol (3.79 g, 37.8 mmol, *E*:*Z*, 98:2 by GLC) and Et_3N (7.88 mL, 56.7 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C under Ar. MsCl (4.76 g, 41.6 mmol) was added dropwise, and the solution was stirred for 15 min at 0 °C and for 15 min at 25 °C and then hydrolyzed with ice water. The resultant solution was diluted with CH_2Cl_2 (100 mL), washed successively with HCl 10% w/w (75 mL), saturated aqueous $NaHCO_3$, (75 mL) and H_2O (2 × 75 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude mesylate as an oil. The mesylate was added to a solution of NaI (14.2 g, 94.5 mmol) in acetone (80 mL) and heated to reflux for 14 h. After cooling to room temperature, the reaction mixture was diluted with petrol, washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo to give pure (*E*)-6-iodo-2-hexene (6.40 g, 81%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.61−5.27 (2H, m), 3.20 (2H, t, J = 5.0 Hz), 2.11 (2H, q, J = 7.0 Hz), 1.92−1.79 (2H, m), 1.76 (3H, d, J = 5.5 Hz).

(*E*)-4-Oxodec-8-enoic Acid (8). A stirred solution of 2,3-dihydrofuran (2.99 g, 42.7 mmol) in THF (25 mL) was cooled to −78 °C before dropwise addition of *t*-BuLi (21.5 mL of a 1.7 M solution in pentane, 36.1 mmol) via cannula. The solution was warmed to −5 °C over 1 h before being recooled to −78 °C. (*E*)-6-Iodo-2-hexene (6.32 g, 30.1 mmol) was added dropwise via syringe, and the resulting solution was warmed to 25 °C and then stirred for 16 h. The reaction mixture was recooled to 0 °C and quenched by careful addition of saturated aq NH_4Cl solution (25 mL). The aqueous phase was extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried ($MgSO_4$) before concentration under reduced pressure. The resultant crude alkylated dihydrofuran was dissolved in THF (80 mL) and Jones' reagent[17] (32.1 mL of a 2.7 M aq solution) was added dropwise with vigorous stirring. After 18 h the reaction mixture was diluted with Et_2O (75 mL) and H_2O (75 mL) and stirred vigorously for 30 min. The aqueous phase was separated and extracted with Et_2O (4 × 50 mL), and the combined organic components were washed with H_2O (3 × 75 mL) and extracted with 10% aq NaOH solution (4 × 50 mL). The combined basic portions were cooled to 0 °C and acidified to pH 1 with concentrated HCl. The cloudy aqueous component was extracted with CH_2Cl_2 (4 × 50 mL) and the combined organic components dried ($MgSO_4$). Concentration under reduced pressure gave the keto acid **8** as a cream solid (2.27 g, 43% over 2 steps). Mp 45 °C; IR (KBr disk) 3375, 2934, 1699, 1380 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.53−5.27 (2H, m), 2.77−2.60 (4H, m), 2.44 (2H, t, J = 7.4 Hz), 1.98 (2H, q, J = 6.7 Hz), 1.72−1.59 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.0, 178.7, 130.5, 126.1, 41.8, 36.7, 31.8, 27.6, 23.3, 17.8; MS (CI+)-*m*/*z* 202 (M + NH_4^+, 100), 185 (M + H^+, 29), 184 (M, 11), 158 (82); HRMS (ES, [M + NH_4]$^+$) calcd 202.1443, measured 202.1443.

***tert*-Butyl (*E*)-3,6-dioxododec-10-enoate (15).** To a stirred solution of (*E*)-4-oxodec-8-enoic acid (2.25 g, 12.2 mmol) in THF

(24) Krief, A.; Kenda, B.; Barbeaux, P.; Guillet, E. *Tetrahedron* **1994**, *50*, 7177−7192.

(60 mL) at 0 °C was added carbonyldiimidazole (2.38 g, 14.7 mmol). After 15 min at 0 °C, the ice bath was removed and the reaction mixture was allowed to warm to 20 °C for 1 h. In a separate flask, mono-*tert*-butyl malonate (4.30 g, 26.9 mmol) was dissolved in THF (60 mL), cooled to −78 °C, and to this was added Bu_2Mg (13.4 mL of a 1.0 M solution in heptane, 13.4 mmol) via syringe. The mixture was stirred for 15 min at −78 °C and then for 1 h at 20 °C. The solvent was removed and the acyl imidazolide was added via cannula to the magnesium salt, rinsing the flask with an additional portion of THF (10 mL). After 18 h the reaction was quenched by the addition of 10% aq citric acid solution (30 mL), the layers were separated, and the aqueous component was extracted with Et_2O (2 × 60 mL). The combined organic components were washed with saturated aq $NaHCO_3$ solution (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography (SiO_2, petrol/Et_2O 8:2; $R_f = 0.17$) to afford *tert*-butyl (*E*)-3,6-dioxododec-10-enoate **15** as a clear yellow oil (2.06 g, 60%): IR (neat) 2979, 2934, 1738, 1715, 1368 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.41−5.33 (2H, m), 3.38 (2H, s), 2.76−2.68 (4H, m), 2.41 (2H, t, $J = 7.3$ Hz), 1.93 (2H, q, $J = 6.4$ Hz), 1.68−1.57 (5H, m), 1.44 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.0, 202.0, 166.3, 130.3, 125.7, 81.9, 50.6, 41.9, 36.2, 36.0, 31.8, 27.9, 23.4, 17.8; MS (CI+) *m*/*z* 300 ($M + NH_4^+$, 54), 283 ($M + H^+$, 6), 244 (100); HRMS (ES, [$M + H^+$]) calcd 283.1909, measured 283.1907.

***tert*-Butyl (*E*)-2-Diazo-3,6-dioxododec-10-enoate (25).** To a stirred solution of 3,6-diketoester **15** (2.00 g, 7.08 mmol) and 4-acetamidobenzenesulfonyl azide (1.87 g, 7.79 mmol) in MeCN (35 mL) at 0 °C was added Et_3N (1.09 mL, 9.69 mmol). After 5 h the reaction was quenched by addition of saturated aq NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (20 mL), and the organic components were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude yellow oil was purified by flash chromatography (SiO_2, petrol/Et_2O 9:1, $R_f = 0.2$) to afford *tert*-butyl (*E*)-2-diazo-3,6-dioxododec-10-enoate **25** (1.95 g, 89%) as a yellow oil: IR (neat) 2978, 2934, 2132, 1715, 1655, 1369 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.41−5.37 (2H, m), 3.08 (2H, t, $J = 6.0$ Hz), 2.71 (2H, t, $J = 6.2$ Hz), 2.45 (2H, t, $J = 7.4$ Hz), 2.01−1.93 (2H, m), 1.67−1.60 (5H, m), 1.51 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.3, 191.7, 160.5, 130.5, 125.7, 83.1, 42.0, 36.1, 34.2, 31.9, 28.3, 23.5, 17.9; MS (CI+) *m*/*z* 326 ($M + NH_4^+$, 12), 309 ($M + H^+$, 27), 300 (48), 270 (88), 244 (100), 200 (85); HRMS (ES, [$M + H]^+$) calcd 309.1814, measured 309.1812.

Synthesis of 2-Diazo-3,6-diketodiester (33) by Cross-Metathesis. (*E*)-7,10-Dioxododec-2-enedioic Acid 12-*tert*-Butyl Ester 1-Methyl Ester (23). Grubbs' catalyst (see Scheme 3)[18] (145 mg, 0.17 mmol) was placed in a dry flask, fitted with a condenser, and dry CH_2Cl_2 (20 mL) was added. A solution of *tert*-butyl 3,6-dioxoundec-10-enoate **49**[19] (915 mg, 34.1 mmol) in CH_2Cl_2 (5 mL) and methyl acrylate (615 μL, 68.2 mmol) were added simultaneously via syringe, and the mixture was heated to reflux for 14 h under argon. After cooling to 20 °C, the mixture was concentrated in vacuo and purified by column chromatography (SiO_2, petrol/ethyl acetate 8:2, $R_f = 0.15$) to give a colorless liquid (1.07 g, 96%, *E*:*Z* 97:3 by ^1H NMR): ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (1H, dt, $J_{trans} = 15.7$ Hz, $J = 7.0$ Hz), 5.80 (1H, dt, $J_{trans} = 15.7$ Hz, $J = 1.6$ Hz), 3.69 (3H, s, (*E*)-isomer), 3.66 (3H, s, (*Z*)-isomer), 3.36 (2H, s), 2.80−2.77 (2H, m), 2.67−2.63 (2H, m), 2.46 (2H, t, $J = 7.3$ Hz), 2.7 (2H, app. qd, $J = 7.2$ and 1.3 Hz), 1.72 (2H, quint, $J = 7.3$ Hz), 1.43 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 201.9, 166.9, 166.3, 148.3, 121.5, 81.9, 51.4, 50.5, 41.5, 36.3, 36.0, 31.3, 27.9, 21.8.

(*E*)-11-Diazo-7,10-dioxo-dodec-2-enedioic Acid 12-*tert*-Butyl Ester 1-Methyl Ester (33). General procedure as for **25**. The residue, obtained from **23** (1.0 g, 3.1 mmol), was purified by column chromatography (SiO_2, petrol/ethyl acetate 8:2, $R_f = 0.16$) to give a colorless liquid (0.91 g, 84%, *E*:*Z* 97:3 by ^1H NMR): ^1H NMR (400 MHz, C_6D_6) δ 7.00 (1H, dt, $J_{trans} = 15.7$ Hz, $J = 7.0$ Hz), 5.92 (1H, dt, $J_{trans} = 15.7$ Hz, $J = 1.5$ Hz), 3.54 (3H, s, (*E*)-isomer), 3.47 (3H, s, (*Z*)-isomer), 3.18 (2H, t, $J = 6.1$ Hz), 2.39 (2H, t, $J = 6.1$ Hz), 2.04 (2H, t, $J = 7.3$ Hz), 1.86 (2H, m), 1.54 (2H, quint, $J = 7.3$ Hz), 1.36 (9H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 207.1, 191.2, 166.7, 160.7, 148.8, 122.0, 82.5, 76.2, 51.0, 41.5, 36.2, 34.9, 31.6, 28.2, 22.3; MS (CI+) *m*/*z* 370 ($M + NH_4^+$, 6), 344 (100), 314 (18), 288 (66), 270 (12), 244 (27); HRMS (ES, [$M + NH_4]^+$) calcd 370.1978, measured 370.1976.

Typical Procedure for a Cycloaddition Reaction. 7-Carbo*tert*-Butoxy-*endo*-6-methyl-11-oxatricyclo[5.3.1.0^{1,5}]-undecan-8-one (35). To a stirred, degassed solution of (*E*)-*tert*-butyl 2-diazo-3,6-dioxododec-10-enoate **25** (100 mg, 0.32 mmol) in dry hexane (5 mL) at 25 °C was added Rh_2(*R*-DDBNP)$_4$ (9.5 mg, 0.003 mmol). After the reaction was complete (50 min, TLC monitoring), the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, petrol/Et_2O 8:2, $R_f = 0.17$) to afford cycloadduct **35** as a colorless oil (71.6 mg, 63%; Scheme 4): $[\alpha]^{24}_D$ +34.9 ($c = 1.0$ in $CHCl_3$); IR (neat) 2942, 1740, 1709, 1448, 1368 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.66−2.59 (1H, m), 2.45−2.34 (2H, m), 2.20 (1H, quint, $J = 7.1$ Hz), 2.09−2.03 (2H, m), 1.91−1.78 (3H, m), 1.68−1.65 (1H, m), 1.60−1.56 (1H, m), 1.49 (9H, s), 1.46−1.38 (1H, m), 1.15 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.1, 166.7, 93.5, 91.7, 82.4, 53.6, 49.4, 37.0, 36.1, 33.2, 32.8, 27.9, 24.7, 14.5; MS (CI+) *m*/*z* 298 ($M + NH_4^+$, 12), 281 ($M + H^+$, 4), 242 (100); HRMS (ES, [$M + H]^+$) calcd 281.1753, measured 281.1750.

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Supporting Information Available: Characterization data of cycloaddition substrates and cycloadducts, chiral GC conditions for all cycloadducts, and copies of ^1H and ^{13}C NMR spectra for all novel cycloaddition substrates and cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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