

## Catalytic Enantioselective [3 + 2]-Cycloadditions of Diazoketone-Derived Aryl-Substituted Carbonyl Ylides

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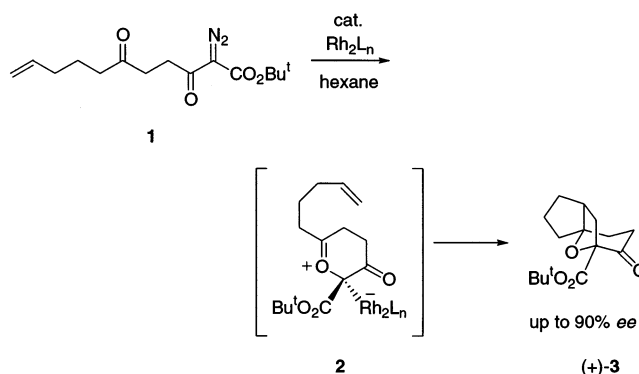
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An evaluation of  $\alpha$ -aryl- $\alpha$ -diazodiones in tandem carbonyl ylide formation–enantioselective [3 + 2]-cycloaddition reactions is described. Such substrates were designed to allow investigation of the electronic characteristics of the dipole upon asymmetric induction. Intramolecular cycloadditions (with a tethered alkene dipolarophile) were found to occur in good to quantitative yields, with a difference in ee exhibited by the two electronically different diazodiones **8** and **9**. Intermolecular cycloadditions using diazodiones **12** and **13** with DMAD and arylacetylenes **16–18** again demonstrated that electronics play a key role in determining the outcome of the cycloaddition reactions. Enantioselectivities of up to 76% were observed.

An attractive approach to reduced furans (and other five-membered oxygen-containing heterocycles) is 1,3-dipolar cycloaddition of a  $\pi$ -bond with a carbonyl ylide.<sup>1</sup> Intramolecular carbonyl ylide formation, usually by metal-catalyzed decomposition of a diazocarbonyl compound (e.g. **1**), followed by cycloaddition, offers the opportunity to control up to four stereocenters. Despite the obvious value of this class of 1,3-dipolar cycloadditions to natural product synthesis<sup>2</sup> (e.g. zaragozic acid<sup>3</sup> and *cis*-nemorensc acids<sup>4</sup>), only recently have examples been reported of enantioselective tandem carbonyl ylide formation–cycloaddition.<sup>5</sup> In contrast to other metal-catalyzed transformations of diazocarbonyl compounds, e.g. enantioselective insertions and cyclopropanations,

### SCHEME 1



where it is evident that an intermediate metal-complexed carbene can directly exert an influence on selectivity, the situation with potentially asymmetric ylide transformations is more complex.<sup>5a</sup> For instance, 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. Alternatively, if a chiral, non-racemic catalyst were to remain associated (e.g. as shown in ylide **2**, Scheme 1), then there is the possibility of achieving an enantioselective cycloaddition reaction. We reported the first example of enantioselective tandem carbonyl ylide formation–cycloaddition in 1997, for the intramolecular process shown in Scheme 1.<sup>6</sup> Enantiomeric excesses of up to 52% were achieved using Davies' prolinic catalyst  $\text{Rh}_2(\text{S-DOSP})_4$  **47** (Figure 1) in hexane. After this initial result, the binaphthyl phosphate cata-

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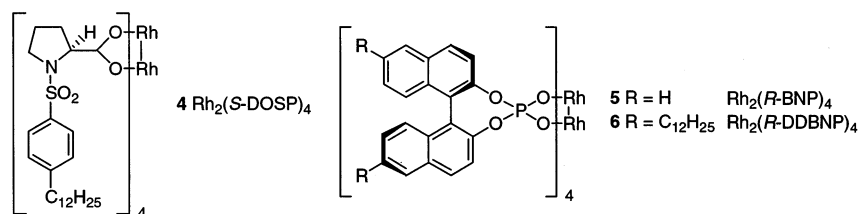
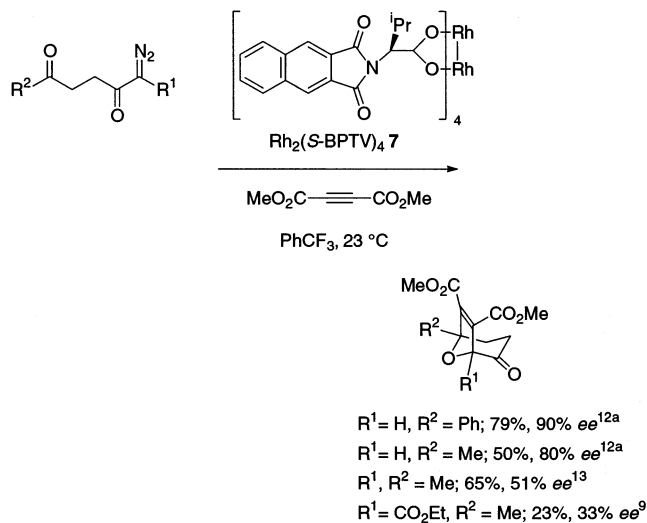


FIGURE 1.

lysts  $\text{Rh}_2(\text{R-BNP})_4$  **5**<sup>8</sup> and  $\text{Rh}_2(\text{R-DDBNP})_4$  **6** (Figure 1) were found capable of delivering improved ee values of up to 90% for cycloadduct **3**.<sup>9</sup>

Enantioselective tandem carbonyl ylide formation–intermolecular cycloadditions have been reported by research groups led by Doyle,<sup>10</sup> Ibata,<sup>11</sup> and Hashimoto.<sup>12</sup> The asymmetric induction in these cycloadditions was low (<30% ee), aside from the work of Hashimoto using  $\alpha$ -diazoketones with DMAD as the dipolarophile, where ee values up to 92% were reported (Scheme 2; the absolute sense of predominant asymmetric induction was not determined).<sup>12a</sup>

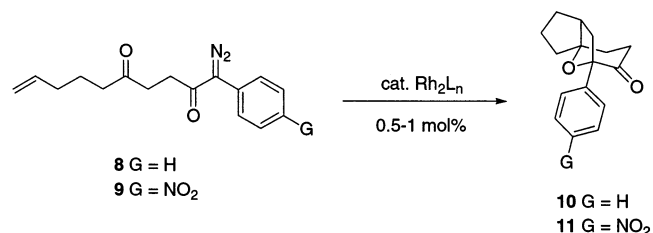
## SCHEME 2



The aim of the work described herein was to develop a better understanding of the factors affecting asymmetric induction in this emerging asymmetric process. This study has involved the synthesis and examination of a new type of diazocarbonyl substrate in both intra- and intermolecular cycloadditions, which generate cycloadducts in up to 76% ee.<sup>13</sup> To begin to elucidate the factors influencing enantioselectivity, we focused initially on electronic effects within the dipole. Work by Hash-

imoto et al.<sup>12a</sup> and ourselves<sup>9,13</sup> (Scheme 2) illustrates that the steric and/or electronic nature of the dipole has an important bearing upon the level of asymmetry induced and warranted further investigation.  $\alpha$ -Aryl- $\alpha$ -diazodiones (e.g. Schemes 3 and 4)<sup>14</sup> were selected as test substrates, since substituent variation within the aryl group (e.g., *p*-methoxy or *p*-nitro groups) allows electronic perturbations on the system to be analyzed without concomitant alteration in the steric environment of the dipole. However, there is only minimal literature precedence for the reactions of  $\alpha$ -aryl- $\alpha$ -diazoketones under rhodium(II) catalysis.<sup>15</sup> C–H insertion and cyclopropanation reactions of such substrates have been reported by Mateos.<sup>16</sup> The only observation to date of enantioselectivity was made by McKervery et al., in which an intramolecular C–H insertion occurred in 45% ee.<sup>17</sup> Until recently, there were no reported examples of tandem carbonyl ylide type formation–cycloaddition reactions of  $\alpha$ -aryl- $\alpha$ -diazoketones. In 1999, Padwa et al. published studies with such substrates in which cycloadditions occurred via “aromatic” carbonyl ylides (oxidopyryliums).<sup>18</sup> Although not strictly comparable to carbonyl ylides formed from  $\alpha$ -aryl- $\alpha$ -diazodiones, this was an encouraging precedent.

## SCHEME 3



Our studies on diazodiones commenced with a simple tethered alkene as the dipolarophile (Scheme 3), designed to undergo intramolecular cycloaddition, analogous to our original work on  $\alpha$ -diazo- $\beta$ -keto esters (Scheme 1).<sup>6,9</sup>

(14) See Supporting Information for details.

(15) This is in stark contrast with  $\alpha$ -aryl- $\alpha$ -diazoacetates, which have been comprehensively examined in most transformations of diazocarbonyl compounds, some with exceptionally high levels of enantioselectivity. Selected examples: (a) Doyle, M. P.; Zhou, Q. L.; Charnsangavej, C.; Longoria, M. A.; McKervery, M. A.; Garcia, C. F. *Tetrahedron Lett.* **1996**, *37*, 4129–4132. (b) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070. (c) Kitagaki, S.; Kinoshita, M.; Takeba, M.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3855–3859. (d) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145–1147.

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Following confirmation of the viability of the substrates **8** and **9** to undergo the desired ylide formation–cycloaddition process on treatment with rhodium(II) acetate in CH<sub>2</sub>Cl<sub>2</sub> at room temperature (Scheme 3, Table 1, entries 1, 13), representatives of the carboxylate and binaphthyl phosphate classes of chiral rhodium(II) catalysts previously shown to impart asymmetric induction in cycloadditions with carbonyl ylides were screened. It was anticipated that the presence of the electron-withdrawing nitro group on diazodione **9** might lead to higher enantioselectivity in the cycloaddition reaction compared with diazodione **8**, since the former would resemble more electronically the successful ester-substituted diazodione **1** (Scheme 1).

**TABLE 1.** Effect of Experimental Conditions on the Cycloadditions of Unsaturated Diazodiones **8** and **9**

| entry | diazo dione | catalyst                               | temp (°C) | solvent                         | yield (%) | ee <sup>a</sup> (%) | [α] <sub>D</sub> <sup>b</sup> |
|-------|-------------|--|-----------|---------------------------------|-----------|---------------------|-------------------------------|
| 1     | <b>8</b>    | Rh <sub>2</sub> (OAc) <sub>4</sub>     | 25        | CH <sub>2</sub> Cl <sub>2</sub> | 77        |                     |                               |
| 2     | <b>8</b>    | Rh <sub>2</sub> (S-DOSP) <sub>4</sub>  | 25        | CH <sub>2</sub> Cl <sub>2</sub> | 71        | 5                   | +3.1                          |
| 3     | <b>8</b>    | Rh <sub>2</sub> (S-DOSP) <sub>4</sub>  | 25        | hexane                          | 75        | 12                  | +4.6                          |
| 4     | <b>8</b>    | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | 25        | hexane                          | 41        | 30                  | +14.8                         |
| 5     | <b>8</b>    | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | reflux    | hexane                          | 81        | 19                  | +8.3                          |
| 6     | <b>8</b>    | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | 25        | PhCF <sub>3</sub>               | 67        | 6                   | -3.2                          |
| 7     | <b>8</b>    | Rh <sub>2</sub> (R-DDBNP) <sub>4</sub> | reflux    | hexane                          | 87        | 19                  | +7.9                          |
| 8     | <b>8</b>    | Rh <sub>2</sub> (R-DDBNP) <sub>4</sub> | 25        | hexane                          | 87        | 35                  | +14.0                         |
| 9     | <b>8</b>    | Rh <sub>2</sub> (R-DDBNP) <sub>4</sub> | 25        | CH <sub>2</sub> Cl <sub>2</sub> | 51        | 10                  | +3.8                          |
| 10    | <b>8</b>    | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | 25        | PhCF <sub>3</sub>               | 74        | 14                  | -6.3                          |
| 11    | <b>8</b>    | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | 25        | hexane                          | 49        | 11                  | -4.8                          |
| 12    | <b>8</b>    | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | 25        | CH <sub>2</sub> Cl <sub>2</sub> | 50        | 7                   | -2.4                          |
| 13    | <b>9</b>    | Rh <sub>2</sub> (OAc) <sub>4</sub>     | 25        | CH <sub>2</sub> Cl <sub>2</sub> | quant     |                     |                               |
| 14    | <b>9</b>    | Rh <sub>2</sub> (S-DOSP) <sub>4</sub>  | 25        | hexane                          | quant     | 8                   | +7.0                          |
| 15    | <b>9</b>    | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | reflux    | hexane                          | 97        | 20                  | +10.8                         |
| 16    | <b>9</b>    | Rh <sub>2</sub> (R-DDBNP) <sub>4</sub> | reflux    | hexane                          | quant     | 28                  | +21.7                         |
| 17    | <b>9</b>    | Rh <sub>2</sub> (R-DDBNP) <sub>4</sub> | 25        | hexane                          | quant     | 51                  | +36.1                         |
| 18    | <b>9</b>    | Rh <sub>2</sub> (R-DDBNP) <sub>4</sub> | 25        | CH <sub>2</sub> Cl <sub>2</sub> | 63        | 8                   | +7.4                          |
| 19    | <b>9</b>    | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | 25        | PhCF <sub>3</sub>               | 98        | 13                  | -7.7                          |

<sup>a</sup> Determined by chiral HPLC. <sup>b</sup> c = 0.95–1.15 in CHCl<sub>3</sub>, T = 24–26 °C.

Proline derivative Rh<sub>2</sub>(S-DOSP)<sub>4</sub> **4** (Figure 1), the first catalyst shown to deliver more than 50% ee in the carbonyl ylide formation–intramolecular cycloaddition reaction of α-diazo-β-ketoester **1** (Scheme 1),<sup>9b</sup> delivered good yields of the cycloadduct (+)-**10** (Table 1, entries 2, 3) in both CH<sub>2</sub>Cl<sub>2</sub> (71%) and hexane (75%), but the ee was low in both cases (5% and 12%, respectively). The absolute sense of asymmetric induction was tentatively assigned as that shown in Scheme 3 by analogy with the corresponding ester system (Scheme 1).<sup>9</sup> Enantioselectivity was only marginally better in hexane; ee improvements on changing to a hydrocarbon solvent are usually much more significant with other asymmetric transformations utilizing Rh<sub>2</sub>(S-DOSP)<sub>4</sub> **4**.<sup>7,9b</sup> With diazodione **9** and Rh<sub>2</sub>(S-DOSP)<sub>4</sub> **4**, a quantitative yield of cycloadduct (+)-**11** was obtained (Table 1, entry 14), but with similarly low ee (8%) to the unsubstituted system **8**.

Attention next turned to binaphthyl phosphate catalysts **5** and **6** (Figure 1), which had given the highest levels of asymmetric induction with α-diazo-β-ketoester **1** (Scheme 1). Rh<sub>2</sub>(R-BNP)<sub>4</sub> **5** in hexane at room temperature furnished cycloadduct (+)-**10** with 30% ee but in a much decreased yield of 41% (Table 1, entry 4), which is most likely attributable to the poor solubility of this catalyst in hydrocarbon solvent. Indeed, at reflux temperature (where there are no catalyst solubility problems)

the yield almost doubled to 81% (Table 1, entry 5); however, there was a slight erosion in ee to 19%. With diazodione **9**, cycloadduct (+)-**11** was produced with essentially identical enantiomeric excess (20%, Table 1, entry 15). A switch to Rh<sub>2</sub>(R-DDBNP)<sub>4</sub> **6** under the same conditions demonstrated that the two cycloadducts could form with different levels of asymmetric induction using the same catalyst; phenyldiazodione **8** delivered cycloadduct in 19% ee, compared with 28% ee from nitrophenyldiazodione **9** (Table 1, entries 7, 16). As catalyst **6** was designed for its solubility in hydrocarbon solvents, ambient temperature could also be used. The difference in cycloadduct ee was now more pronounced: 35% ee for phenyl-substituted cycloadduct (+)-**10** and 51% ee for the nitrophenyl-substituted cycloadduct (+)-**11** (Table 1, entries 8, 17). However, changing the solvent to CH<sub>2</sub>Cl<sub>2</sub> with Rh<sub>2</sub>(R-DDBNP)<sub>4</sub> **6** removed differences in ee between the two cycloadditions (Table 1, entries 9, 18).

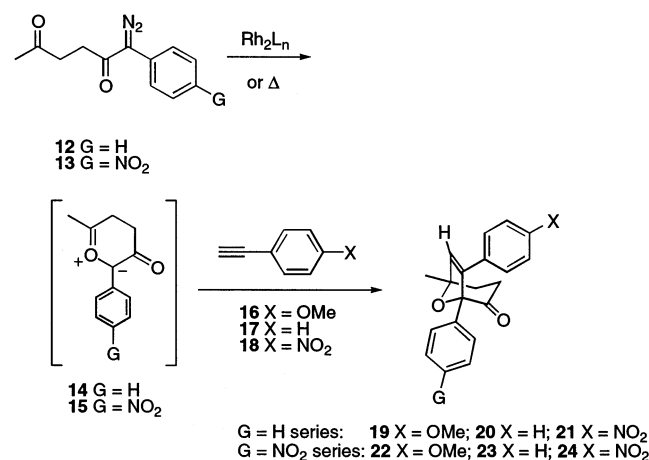
Application of Hashimoto's optimum conditions<sup>12a</sup> to the aryl diazodione systems delivered good to excellent yields of cycloadduct (74% with **8**, Table 1, entry 10 and 98% with **9**, entry 19). However, ee values were again low and at the same level. Other solvents screened in conjunction with Rh<sub>2</sub>(S-BPTV)<sub>4</sub> **7** and diazodione **8** (Table 1, entries 11, 12) resulted in lower yields and ee values.

From the results recorded in Table 1 it is apparent that most of the catalysts deliver similar levels of ee for both systems. However, it was interesting to find the anticipated difference in levels of asymmetric induction between the two systems, although it was somewhat surprising that only one of the catalysts screened [Rh<sub>2</sub>(R-DDBNP)<sub>4</sub> **6**] exhibited this effect. The absolute values of ee are modest, but a difference in ee between cycloadducts arising from the two catalyst-associated ylides with the same tethered alkene dipolarophile exists. This provides the first unambiguous demonstration that electronic effects can play a role in determining the level of asymmetric induction in such cycloaddition processes.

Removal of the tethered alkene from the substrates provided ready opportunity for variation of the dipolarophile electronics. Only a small range of dipolarophiles have been examined in asymmetric intermolecular cycloadditions of carbonyl ylides, and of these, only DMAD, used by Hashimoto, has met with any real success.<sup>12</sup> However, with this dipolarophile and α-aryl-α-diazodione **12**, only modest levels of asymmetric induction were observed using a range of catalysts [up to 36% ee with Rh<sub>2</sub>(S-BPTV)<sub>4</sub> **7** in PhCF<sub>3</sub>], and essentially no enantioinduction was seen with α-aryl-α-diazodione **13**.<sup>14</sup> These contrasting results led us to consider that when the dipole and dipolarophile have similar electronic characteristics, the ee is lower than when they oppose. To pursue this analysis further, we considered it important to examine cycloaddition reactions using the same substrates, but with a less electron deficient dipolarophile. Arylacetylenes were selected (**16**–**18**, Scheme 4) since, similarly to the diazo substrates examined, introduction of substituents at the 4-position on the aryl group could allow investigation of solely electronic variations. With these unsymmetrical dipolarophiles, interest also lay in the regiochemical outcome of the cycloaddition reactions.



## SCHEME 4



Both substrates **12** and **13** underwent the tandem catalytic ylide generation–intermolecular cycloaddition process with Rh<sub>2</sub>(OAc)<sub>4</sub> in toluene to deliver the cycloadducts from 4-methoxyphenylacetylene (**16**), phenylacetylene (**17**), and 4-nitrophenylacetylene (**18**) in good to excellent yields (Scheme 4, Table 2). Only single regioisomers were observed in the crude reaction mixtures (one singlet in the crude <sup>1</sup>H NMR spectra at approximately δ 6.5 for the olefinic proton). Once isolated, the cycloaddition regiochemistry was determined to be the same for all cycloadducts (that shown in Scheme 4) by 2D NOE NMR experiments, which showed a strong correlation between the methyl group and the olefinic proton in each case. Aromatic π–π interactions may contribute to the origin of the regiochemistry.<sup>19</sup> In the absence of catalyst and using heat to decompose the diazodiones, the cycloadducts were formed with the same regioselectivity, but in much reduced yields (Table 2, yields in parentheses).

**TABLE 2. Racemic Cycloadditions of Diazodiones **12** and **13** with Arylacetylenes **16–18****

| entry | diazodione | dipolarophile | cycloadduct | yield (%) <sup>a</sup> |
|-------|------------|---------------|-------------|------------------------|
| 1     | <b>12</b>  | <b>16</b>     | <b>19</b>   | 76 (8)                 |
| 2     | <b>12</b>  | <b>17</b>     | <b>20</b>   | 60 (2)                 |
| 3     | <b>12</b>  | <b>18</b>     | <b>21</b>   | 82 (8)                 |
| 4     | <b>13</b>  | <b>16</b>     | <b>22</b>   | 89 (17)                |
| 5     | <b>13</b>  | <b>17</b>     | <b>23</b>   | 82 (19)                |
| 6     | <b>13</b>  | <b>18</b>     | <b>24</b>   | 58 (17)                |

<sup>a</sup> Yield in the absence of catalyst is indicated in parentheses.

To examine any effect a catalyst might have on the relative rates of the cycloadditions and to establish if there is a correlation between the rate of cycloaddition and asymmetric induction, competition experiments were devised. Each diazodione was individually heated in the presence of equal quantities (5 equiv) of all three acetylenes and the product ratio determined. The <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) of the crude reaction mixture displayed clear, distinct singlets for the olefinic proton of each cycloadduct. Integration then gave the relative amounts generated from each acetylene (Table 3). Similar experi-

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**TABLE 3. Cycloadduct Partitioning in Competition Reactions Employing Arylacetylenes **16–18****

| entry <sup>a</sup> | diazodione | catalyst                                       | solvent           | cycloadduct ratio <sup>b</sup> |                        |                        |
|--------------------|------------|--|-------------------|--------------------------------|------------------------|------------------------|
|                    |            |  |                   | <b>19</b> or <b>22</b>         | <b>20</b> or <b>23</b> | <b>21</b> or <b>24</b> |
| 1                  | <b>12</b>  | none   | toluene           | 1                              | 1                      | 4                      |
| 2                  | <b>12</b>  | Rh <sub>2</sub> (OAc) <sub>4</sub>             | toluene           | 1                              | 1                      | 9                      |
| 3 <sup>c</sup>     | <b>12</b>  | Rh <sub>2</sub> ( <i>R</i> -BNP) <sub>4</sub>  | toluene           | 1.5                            | 1                      | 8                      |
| 4 <sup>c</sup>     | <b>12</b>  | Rh <sub>2</sub> ( <i>S</i> -BPTV) <sub>4</sub> | PhCF <sub>3</sub> | 1                              | 1                      | 11                     |
| 5                  | <b>13</b>  | none   | toluene           | 2.5                            | 1                      | 2                      |
| 6                  | <b>13</b>  | Rh <sub>2</sub> (OAc) <sub>4</sub>             | toluene           | 1.5                            | 1                      | 1                      |
| 7 <sup>c</sup>     | <b>13</b>  | Rh <sub>2</sub> ( <i>R</i> -BNP) <sub>4</sub>  | toluene           | 2                              | 1                      | 1                      |
| 8 <sup>c</sup>     | <b>13</b>  | Rh <sub>2</sub> ( <i>S</i> -BPTV) <sub>4</sub> | PhCF <sub>3</sub> | 2.5                            | 1                      | 2.5                    |

<sup>a</sup> Carried out at room temperature, apart from entries 1 and 5 at reflux. <sup>b</sup> Entries 1–4 refer to **19:20:21**; entries 5–8 refer to **22:23:24**. <sup>c</sup> The ee values obtained were the same as when each acetylene was used in isolation (see Table 4).

ments were then carried out (at room temperature) with selected dirhodium catalysts.

For phenyldiazodione **12**, in the absence of a catalyst, reaction with nitrophenylacetylene **18** dominated (Table 3, entry 1), whereas for nitrophenyldiazodione **13**, reaction with methoxy- and nitrophenylacetylenes (**16** and **18**) was slightly favored over phenylacetylene **17** (Table 3, entry 5). Cycloaddition competition experiments with phenyldiazodione **12** under dirhodium catalysis gave a significantly greater proportion of cycloaddition from nitrophenylacetylene **18**. All three catalysts showed a similar product profile (Table 3, entries 2–4). These results indicate that the catalyst may be influencing the energies of the molecular orbitals of the ylide. However, with nitrophenyldiazodione **13**, there was no significant change in cycloadduct profile under dirhodium catalysis, suggesting that during cycloaddition the catalysts do not strongly perturb the molecular orbital energies of the comparatively more electron deficient ylide derived from **13**. The possibility of interaction between the catalyst and the alkynes also cannot be discounted.<sup>20</sup>

To account for the observations in the above competition reactions, at least in the absence of catalyst, the HOMO–LUMO energy gaps between the two ylides **14** and **15** (Scheme 4) and the acetylenic dipolarophiles were obtained from density functional theory (DFT) calculations (geometries optimized at the B3LYP/6-31G(d) level).<sup>14</sup> The trend in reaction rates was well-reproduced by the calculations in that the energy gap for nitrophenylacetylene **18** and ylide **14** is much smaller than for the other two alkynes, explaining the greater amount of cycloadduct derived from this reactant combination in the competition experiment. With ylide **15** the energy gaps are fairly similar with all three alkynes, as reflected by the product ratio.

Having determined the relative rates of cycloaddition between diazodiones **12** and **13** with three aryldiacetylenes **16–18**, a series of experiments were carried out to determine the influence of the dipole and dipolarophile on asymmetric induction. Cycloadditions were performed

(20) For UV studies demonstrating association between electron-deficient (perfluorinated) rhodium carboxylate catalysts and alkenes, see: (a) Doyle, M. P.; Colman, M. R.; Chinn, M. S. *Inorg. Chem.* **1984**, *23*, 3684–3685. (b) Doyle, M. P.; Mahapatro, S. N.; Caughey, A. C.; Chinn, M. S.; Colman, M. R.; Harn, N. K.; Redwine, A. E. *Inorg. Chem.* **1987**, *26*, 3070–3072. However, with acetylenes **16–18** and Rh<sub>2</sub>(*R*-BNP)<sub>4</sub>, UV titrations indicated that association is not significant, see: Glen, R. D. Phil. Thesis, University of Oxford, 2002.

**TABLE 4. Effect of Experimental Conditions on the Cycloadditions of Diazodiones **12** and **13** with Arylacetylenes **16**–**18****

| entry           | dipolar-ophile | diazo dione | catalyst                               | solvent                         | yield (%) | ee (%) <sup>a</sup> | [α] <sub>D</sub> <sup>b</sup> |
|-----------------|----------------|-------------|--|---------------------------------|-----------|---------------------|-------------------------------|
| 1               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (OAc) <sub>4</sub>     | toluene                         | 60        |                     |                               |
| 2               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (S-DOSP) <sub>4</sub>  | CH <sub>2</sub> Cl <sub>2</sub> | 15        | 3                   | +2.4                          |
| 3               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (S-DOSP) <sub>4</sub>  | toluene                         | 29        | 5                   | +8.7                          |
| 4               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | CH <sub>2</sub> Cl <sub>2</sub> | 25        | 3                   |                               |
| 5               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | toluene                         | 37        | 38                  | −63.1                         |
| 6               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | PhCF <sub>3</sub>               | 47        | 28                  | +48.7                         |
| 7               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (OAc) <sub>4</sub>     | PhC≡CH                          | 60        |                     |                               |
| 8               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | PhC≡CH                          | 25        | 38                  | −47.5                         |
| 9               | <b>17</b>      | <b>12</b>   | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | PhC≡CH                          | 39        | 36                  | +67.5                         |
| 10              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (OAc) <sub>4</sub>     | toluene                         | 82        | −                   |                               |
| 11              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (S-DOSP) <sub>4</sub>  | CH <sub>2</sub> Cl <sub>2</sub> | 34        | 2                   | +5.3                          |
| 12              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (S-DOSP) <sub>4</sub>  | toluene                         | 34        | 3                   | +6.2                          |
| 13              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | CH <sub>2</sub> Cl <sub>2</sub> | 22        | 29                  | −57.4                         |
| 14              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | toluene                         | 54        | 48                  | −105.5                        |
| 15              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | PhCF <sub>3</sub>               | 69        | 43                  | +97.0                         |
| 16              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (OAc) <sub>4</sub>     | PhC≡CH                          | 98        |                     |                               |
| 17              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | PhC≡CH                          | 73        | 66                  | −132.0                        |
| 18              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (R-DDBNP) <sub>4</sub> | PhC≡CH                          | 80        | 66                  | −114.6                        |
| 19 <sup>c</sup> | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (R-DDBNP) <sub>4</sub> | PhC≡CH                          | 83        | 76                  | −154.4                        |
| 20              | <b>17</b>      | <b>13</b>   | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | PhC≡CH                          | 49        | 45                  | +88.3                         |
| 21              | <b>16</b>      | <b>12</b>   | Rh <sub>2</sub> (OAc) <sub>4</sub>     | toluene                         | 76        |                     |                               |
| 22              | <b>16</b>      | <b>12</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | CH <sub>2</sub> Cl <sub>2</sub> | 22        | 3                   | +3.0                          |
| 23              | <b>16</b>      | <b>12</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | toluene                         | 41        | 10                  | +12.2                         |
| 24              | <b>16</b>      | <b>12</b>   | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | PhCF <sub>3</sub>               | 43        | 3                   | +2.7                          |
| 25              | <b>16</b>      | <b>13</b>   | Rh <sub>2</sub> (OAc) <sub>4</sub>     | toluene                         | 89        |                     |                               |
| 26              | <b>16</b>      | <b>13</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | CH <sub>2</sub> Cl <sub>2</sub> | 41        | 0                   | −6.7                          |
| 27              | <b>16</b>      | <b>13</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | toluene                         | 48        | 18                  | −43.8                         |
| 28              | <b>16</b>      | <b>13</b>   | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | PhCF <sub>3</sub>               | 65        | 40                  | +70.7                         |
| 29              | <b>18</b>      | <b>12</b>   | Rh <sub>2</sub> (OAc) <sub>4</sub>     | toluene                         | 60        |                     |                               |
| 30              | <b>18</b>      | <b>12</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | CH <sub>2</sub> Cl <sub>2</sub> | 43        | 24                  | +22.0                         |
| 31              | <b>18</b>      | <b>12</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | toluene                         | 50        | 31                  | +27.6                         |
| 32              | <b>18</b>      | <b>12</b>   | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | PhCF <sub>3</sub>               | 73        | 1                   | +2.0                          |
| 33              | <b>18</b>      | <b>13</b>   | Rh <sub>2</sub> (OAc) <sub>4</sub>     | toluene                         | 82        |                     |                               |
| 34              | <b>18</b>      | <b>13</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | CH <sub>2</sub> Cl <sub>2</sub> | 26        | 35                  | +50.1                         |
| 35              | <b>18</b>      | <b>13</b>   | Rh <sub>2</sub> (R-BNP) <sub>4</sub>   | toluene                         | 33        | 31                  | +49.0                         |
| 36              | <b>18</b>      | <b>13</b>   | Rh <sub>2</sub> (S-BPTV) <sub>4</sub>  | PhCF <sub>3</sub>               | 72        | 38                  | +54.4                         |

<sup>a</sup> Determined by chiral HPLC. <sup>b</sup>  $c = 0.4$ – $1.12$  in CHCl<sub>3</sub>,  $T = 20$ – $25$  °C. <sup>c</sup> At 0 °C.

with each diazo dione **12** and **13** and dipolarophile **16**–**18** combination (Scheme 4, Table 4).

For phenylacetylene (**17**), Rh<sub>2</sub>(S-DOSP)<sub>4</sub> **4** gives low yields of essentially racemic cycloadduct **20** with both diazo substrates **12** and **13** in chlorinated and hydrocarbon solvents (Table 4, entries 2, 3, 11, 12). Rh<sub>2</sub>(R-BNP)<sub>4</sub> **5** and Rh<sub>2</sub>(R-DDBNP)<sub>4</sub> **6** were both shown earlier to give ee values in the range of 30–50% with the substrates **8** and **9** containing a tethered alkene as the dipolarophile (Scheme 3, Table 1). It was considered that phenylacetylene (**17**) might possess similar dipolarophile character to a terminal alkene and therefore favor asymmetric induction with the phosphate catalysts. Hexane as solvent gave the best results for the intramolecular cycloaddition; however, nitrophenyldiazodione **13** proved only sparingly soluble in this solvent. Using CH<sub>2</sub>Cl<sub>2</sub> as solvent with diazo substrate **12** and Rh<sub>2</sub>(R-BNP)<sub>4</sub> **5** gave essentially racemic product **20** in low yield (Table 4, entry 4). The yield remained poor but enantioselectivity improved from 3% to 29% upon changing substrate to **13** (Table 4, entry 13). Switching to the hydrocarbon solvent toluene gave better yields and ee values, as anticipated, for both substrates **12** and **13** with nitro-substituted diazodione **13** delivering cycloadduct **23** in 48% ee (Table 4, entries 5, 14). Rh<sub>2</sub>(S-BPTV)<sub>4</sub> **7** was found to be the most efficient chiral catalyst in terms of yield for each substrate. However, the asymmetric induction observed did

not quite reach the level seen with the phosphate catalyst **5** (Table 4, entries 6, 15). For phenylacetylene (**17**) it can be seen that all the catalysts screened [with the exception of Rh<sub>2</sub>(S-DOSP)<sub>4</sub> **4**] display higher levels of ee for diazodione **12** compared with **13**. These results are consistent with the suggestion made earlier invoking contrasting dipole/dipolarophile electronics for favorable ee.

In contrast to phenylacetylene (**17**), where some ee was observed in CH<sub>2</sub>Cl<sub>2</sub> at least for the nitrophenyl substrate **13**, Rh<sub>2</sub>(R-BNP)<sub>4</sub> **5** gave asymmetric induction with methoxy-substituted phenylacetylene **16** only when used in toluene (Table 4, entries 23, 27). Yields were in the same range as for unsubstituted phenylacetylene (**17**), but the ee values were reduced. This was contrary to expectation, as it was considered that the increased electron richness of the dipolarophile might lead to higher ee. A difference between the two diazo substrates was still exhibited, with the electron-poor diazodione **13** giving higher ee. This difference was more pronounced when Rh<sub>2</sub>(S-BPTV)<sub>4</sub> **7** was employed. A 40% ee was observed (Table 4, entry 28), the same as for phenylacetylene (**17**) with a similar yield.

For 4-nitrophenylacetylene (**18**) the use of Rh<sub>2</sub>(R-BNP)<sub>4</sub> **5** in CH<sub>2</sub>Cl<sub>2</sub> resulted in the formation of enantioenriched product **21** with phenyl-substituted diazodione **12**. The use of toluene as solvent raised the ee slightly from 24% to 31% (Table 4, entries 30, 31). Surprisingly, with diazodione **13** and Rh<sub>2</sub>(R-BNP)<sub>4</sub> **5**, the two solvents delivered cycloadduct **24** with very similar ee values (35 and 31% ee, Table 4, entries 34, 35); furthermore, both substrates **12** and **13** demonstrated the same level of asymmetric induction (31% ee) with the phosphate catalyst **5** in toluene (Table 4, entries 31, 35), whereas CH<sub>2</sub>Cl<sub>2</sub> did exhibit the expected difference with 24% ee compared to 35% ee (Table 4, entries 30, 34). Rh<sub>2</sub>(S-BPTV)<sub>4</sub> **7** also showed a difference in ee, dependent upon the substrate used. Racemic cycloadduct **21** was obtained for the phenyldiazodione **12**, but 38% ee was achieved for the nitrophenyldiazodione **13** (Table 4, entries 32, 36). With both diazodiones there was a large improvement in yield compared to when using Rh<sub>2</sub>(R-BNP)<sub>4</sub> **5** as catalyst.

The differences in ee between cycloadducts arising from the same catalyst-associated ylide with the three different dipolarophiles provide further support that electronic effects play a role in determining the level of asymmetric induction in such cycloaddition processes. Moreover, for the phenyl-substituted dipole, where the competition reactions conclusively ascertained that nitrophenylacetylene **18** was the most reactive dipolarophile (Table 3, entries 3, 4), it has been shown that higher rates of cycloaddition do not lead to better asymmetric induction (e.g. Table 4, entries 5, 23, 31). Thus, a simple reaction scheme whereby a reduction in ee is due to loss of catalyst from the ylide, followed by cycloaddition on the achiral ylide, is shown not to be valid, at least in these experiments.<sup>5a</sup>

From the results in Table 4 discussed so far, it is evident that the highest ee values were generally obtained using phenylacetylene (**17**), and so further experimentation was carried out using **17** as both the dipolarophile and reaction solvent. The use of phenylacetylene (**17**) as solvent had little effect with phenyldiazodione **12**. The yield with Rh<sub>2</sub>(OAc)<sub>4</sub> remained at the 60% observed

with toluene (Table 4, entries 4, 7).  $\text{Rh}_2(R\text{-BNP})_4$  **5** gave the same 38% ee in neat phenylacetylene (**17**) as for toluene (Table 4, entries 5, 8), whereas  $\text{Rh}_2(S\text{-BPTV})_4$  **7** gave a reduced yield but slightly better ee (Table 4, entries 6, 9). The yield with  $\text{Rh}_2(\text{OAc})_4$  was significantly improved to near quantitative when the reaction was carried out in neat phenylacetylene (**17**) with nitrophenyl-substituted substrate **13** (Table 4, entry 16). Also, phenylacetylene (**17**) appeared to be a better solvent than toluene for inducing enantioselectivity with the binaphthyl catalysts and nitrophenyldiazodione **13**. Both phosphate catalysts **5** and **6** gave the same 66% ee (compared with 48% ee for catalyst **5** in toluene), but the yield of cycloadduct **23** was better for the more soluble  $\text{Rh}_2(R\text{-DDBNP})_4$  **6** at 80% (Table 4, entries 14, 17, 18). Lowering the temperature to 0 °C, in combination with  $\text{Rh}_2(R\text{-DDBNP})_4$  **6**, led to the highest ee observed in the current study: 76% with good yield (83%) maintained (Table 4, entry 19).  $\text{Rh}_2(S\text{-BPTV})_4$  **7** gave essentially the same ee values in  $\text{PhCF}_3$  and neat phenylacetylene (**17**) with precursor **13** (Table 4, entries 15, 20) but with a 20% reduction in yield in the latter case.

$\alpha$ -Aryl- $\alpha$ -diazodiones have been shown to undergo tandem ylide formation–cycloaddition processes with both internal and external dipolarophiles. A difference in ee between the two electronically differing substrates **8** and **9** was displayed in intramolecular cycloadditions with a tethered alkene, although only when  $\text{Rh}_2(R\text{-DDBNP})_4$  **6** was used as catalyst in hexane. As anticipated, the more electron-deficient cycloaddition precursor **9** (therefore bearing a closer resemblance to the  $\alpha$ -diazo- $\beta$ -ketoester substrate **1** for which high levels of ee were previously achieved in intramolecular cycloaddition) delivered the higher enantioselectivity. Electronic effects clearly play a role in determining the level of asymmetric

induction in such cycloaddition processes. Intermolecular cycloaddition competition experiments with aryl-substituted carbonyl ylides show that nitrophenylacetylene (**18**) reacts fastest in the cycloaddition process, and DFT calculations<sup>14</sup> concur with this observation. The presence of a Rh(II) catalyst can affect the product ratio. The first asymmetric induction in intermolecular cycloadditions of carbonyl ylides with aryl acetylenes has been observed. Higher rates of cycloaddition have been shown not to lead to better asymmetric induction. The binaphthyl catalysts gave the best enantioselectivities (up to 76% ee), extending their usefulness.<sup>21</sup> These results suggest 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. Further studies are underway to investigate enantioselectivity in such cycloaddition processes.

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**Supporting Information Available:** Full experimental details of syntheses and characterization of cycloaddition substrates and cycloadducts, chiral HPLC conditions for all cycloadducts, copies of <sup>1</sup>H and <sup>13</sup>C spectra for all novel compounds, and DFT studies and Gaussian 98 archive files containing minimized structures and vibrational frequencies for compounds **14**–**18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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