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[3+2] Cycloaddition reactions of arylacetylenes with carbonyl ylides derived from 1-aryl-1-diazohexane-2,5-diones

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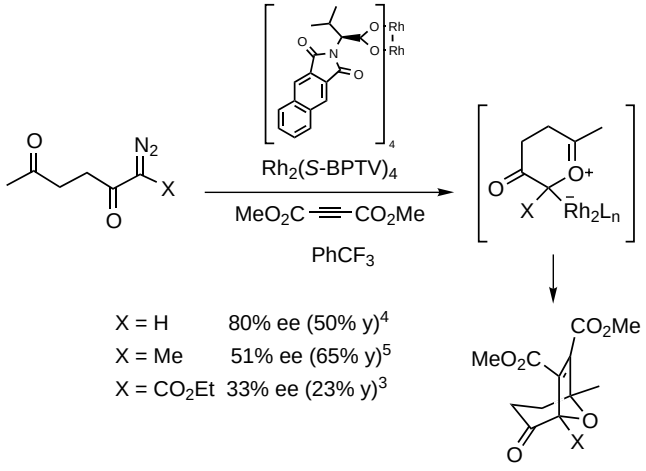
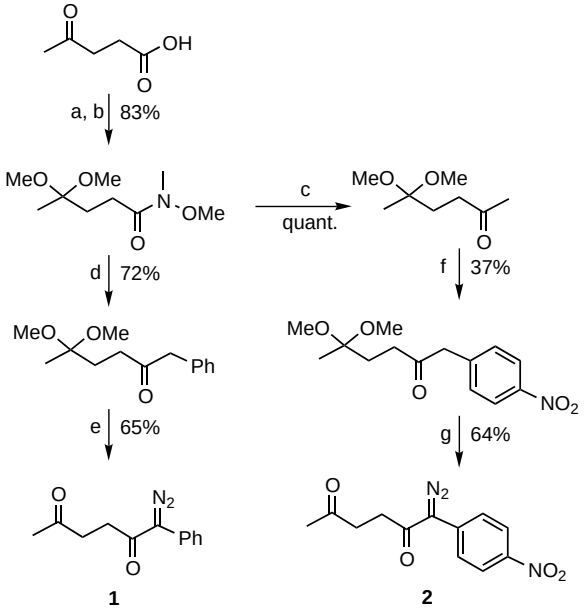
Abstract—The synthesis and 1,3-dipolar cycloaddition reactions of α-aryl-α-diazodiones with aryl acetylenes (up to 76% ee) are described.

There are currently few methods to achieve catalytic enantioselective 1,3-dipolar cycloadditions, despite the potential utility of such asymmetric transformations.[1] Following our report of the first examples of enantioselective tandem carbonyl ylide formation–cycloaddition in 1997,[2] we have been interested in exploring its scope and limitations.[3] In order to begin to elucidate the factors influencing enantioselectivity in this new asymmetric process we focused initially on electronic effects within the dipole. Work by Hashimoto et al. (Scheme 1, X = H)[4] and ourselves (Scheme 1, X = Me,[5] CO_2Et[3]) illustrates that the nature of the dipole (be it steric and/or electronic) has an important bearing upon the level of asymmetry induced and we wished to investigate this further. We selected α-aryl-α-diazodiones (e.g. **1**, Scheme 2) as test substrates, since substituent variation within the aryl group (for example *p*-methoxy or



Scheme 1.



Scheme 2. (a) MeOH, $(MeO)_3CH$, H_2SO_4, reflux, 18 h; (b) Me(MeO)NH·HCl, *i*-PrMgCl, THF −10°C, 2.5 h; (c) MeMgBr, THF, 0°C, 1.5 h; (d) BnMgCl, THF, 0°C, 2 h; (e) 4-$(NHAc)C_6H_4SO_2N_3$, DBU, MeCN, 0°C, 16 h, then 10% citric acid; (f) *t*-BuOK, 4-$(NO_2)C_6H_4CHO$, NH_3, −70°C, 8 h; (g) 4-$(NHAc)C_6H_4SO_2N_3$, Et_3N, MeCN, 0°C, 2 h, then 10% citric acid.

Keywords: asymmetric catalysis; carbonyl ylides; cycloadditions; diazo compounds; rhodium.

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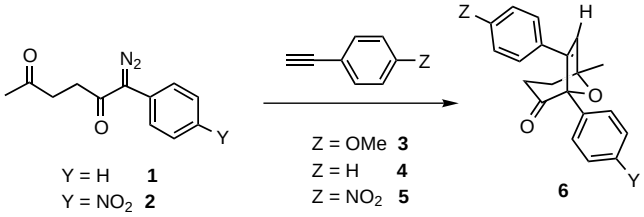
p-nitro groups) allows electronic perturbations on the system to be analysed without concomitant alteration in the steric environment of the dipole. Intermolecular cycloadditions also provided opportunities for ready variation of the dipolarophile electronics using, for example, aryl acetylenes.

The previously unknown α-aryl-α-diazo-containing diones were synthesised from levulinic acid via the sequence in Scheme 2 (attempted preparation of the *p*-methoxy derivative failed due to the instability of the diazodione). For the phenyl diazodione **1**, DBU instead of Et_3N was necessary to effect diazo transfer[6] and the presence of the ketal at the diazo transfer step was crucial to prevent cyclopentenone formation via an intramolecular aldol reaction.[7] For nitrophenyl diazodione **2** an unusual formyl displacement from *p*-nitrobenzaldehyde[8] was used to generate the α-aryl ketone.



Scheme 3.

Table 1. Cycloadditions using $Rh_2(OAc)_4$[a]

Entry	Diazodione	Dipolarophile	Yield[b] (%)
1	**1**	**3**	76
2	**1**	**4**	60
3	**1**	**5**	82
4	**2**	**3**	89
5	**2**	**4**	82
6	**2**	**5**	58

[a] All reactions carried out in toluene (0.05 M) at 25°C with 5 equiv. acetylene and 0.5–1 mol% $Rh_2(OAc)_4$.
[b] Isolated yields.

It was found that, pleasingly, such substrates underwent the tandem catalytic ylide generation–intermolecular cycloaddition process[9] with $Rh_2(OAc)_4$ to deliver the cycloadducts **6** from a range of (commercially available) aryl acetylenes **3**–**5** in good to excellent yields (Scheme 3, Table 1).[10] Only one of the possible regioisomers was observed in each crude reaction mixture and, once isolated, the cycloaddition regiochemistry was determined by NOE experiments to be the same for all cycloadducts (Scheme 3).[11] 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 (2–19%).

In order to examine any effect a catalyst might have on relative rates of the cycloadditions each diazodione was first individually heated in the presence of equal quantities (5 equiv.) of all three acetylenes and the product ratio determined. Similar experiments were then carried out (at room temperature) with $Rh_2(OAc)_4$ and two of the chiral catalysts which are currently best able to deliver asymmetric induction in carbonyl ylide cycloadditions: carboxylate catalyst $Rh_2(S\text{-BPTV})_4$ (shown in Scheme 1) and phosphate catalyst $Rh_2(R\text{-BNP})_4$ (Fig. 1, Table 2).

For phenyl diazodione **1**, in the absence of a catalyst, reaction with nitrophenylacetylene dominated (Table 2, entry 1), whereas for nitrophenyl diazodione **2** reaction with methoxy- and nitrophenylacetylenes were slightly favoured over phenylacetylene (Table 2, entry 5). Cycloaddition competition experiments with phenyl diazodione **1** under dirhodium catalysis gave a significantly greater proportion of cycloaddition from nitrophenylacetylene, with all three catalysts showing a

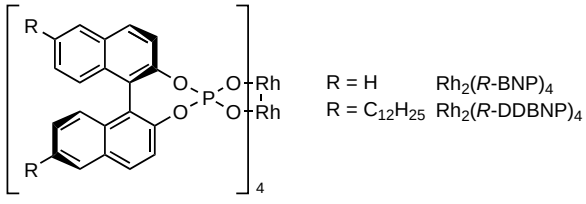


Figure 1.

Table 2. Cycloaddition competition reactions

Entry[a]	Diazodione	Catalyst	Solvent	Cycloadduct ratio[b] from dipolarophile		
				3	**4**	**5**
1	**1**	None	Toluene	1	1	4
2	**1**	$Rh_2(OAc)_4$	Toluene	1	1	9
3	**1**	$Rh_2(R\text{-BNP})_4$	Toluene	1.5	1	8
4	**1**	$Rh_2(S\text{-BPTV})_4$	$PhCF_3$	1	1	11
5	**2**	None	Toluene	2.5	1	2
6	**2**	$Rh_2(OAc)_4$	Toluene	1.5	1	1
7	**2**	$Rh_2(R\text{-BNP})_4$	Toluene	2	1	1
8	**2**	$Rh_2(S\text{-BPTV})_4$	$PhCF_3$	2.5	1	2.5

[a] Carried out at room temperature, apart from entries 1 and 5 at reflux.
[b] Ratios of the three cycloadducts produced could be determined from the ^1H NMR spectrum (C_6D_6) of the crude reaction mixture by integration of the distinct olefinic H singlets.

similar product profile (Table 2, entries 2–4). These results indicate that the catalyst may be influencing the energies of the molecular orbitals of the ylide. However, with nitrophenyl diazodione **2** 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 **2**.

Knowing the relative rates of cycloaddition, a series of experiments were then carried out to determine the influence of the dipole and dipolarophile on asymmetric induction. Cycloadditions were carried out with each diazodione and dipolarophile combination and two solvent–catalyst combinations (Table 3). Yields of cycloadducts are generally lower than those obtained using $Rh_2(OAc)_4$; $Rh_2(S\text{-BPTV})_4$ is slightly more efficient than $Rh_2(R\text{-BNP})_4$ in all cases [except with nitrophenyl dione **2** and nitrophenylacetylene **5** when $Rh_2(S\text{-BPTV})_4$ gives a significant improvement in yield (Table 3, entries 9 and 12)]. Each of the four possible diazo substrate–catalyst interactions will initially generate a catalyst-associated ylide with a certain level of diastereomeric excess; the results indicate that each of these catalyst-associated ylides do not lead to equally enantioenriched cycloadducts with the three acetylenic dipolarophiles [except for the case of the nitrophenyl-substituted dipole and $Rh_2(S\text{-BPTV})_4$ (Table 3, entries 10–12)]. The absolute values of ee are modest, but the differences in ee between cycloadducts arising from the same catalyst-associated ylide and the three different dipolarophiles provide the first unambiguous demonstration 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 was the most reactive dipolarophile (Table 2, entries 3 and 4), it is shown that higher rates of cycloaddition do not lead to better asymmetric induction (Table 3, entries 1–6). [The ees obtained in the competition reactions with $Rh_2(R\text{-BNP})_4$ and $Rh_2(S\text{-BPTV})_4$ were the same as when each acetylene was used in isolation.] 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,[1c] at least in these experiments.

Whilst only modest levels of asymmetric induction are recorded in Table 3, these are the first examples of phenyl-substituted dipoles and of acetylenes (other than diester-substituted systems) in such cycloadditions and provide encouragement to investigate further substrate and catalyst combinations in this newly emerging enantioselective process. Indeed, the following experiments show that improvement in asymmetric induction with these types of substrates is certainly possible. From Table 3, it is evident that the highest ees were generally obtained using phenylacetylene as dipolarophile and further experimentation established that using phenylacetylene as both the dipolarophile and reaction solvent proved advantageous, with 66% ee (yield 73%) being obtained at room temperature from the nitrophenyl-substituted diazodione **2** and $Rh_2(R\text{-BNP})_4$. Changing to the more hydrocarbon-soluble $Rh_2(R\text{-DDBNP})_4$[3] improved the yield to 80%, whilst the ee remained the same (66%). At 0°C the ee increased to 76% (yield 83%); however, further lowering of the temperature totally inhibited diazo decomposition.

In summary, a route to α-aryl-α-diazodiones has been established; such substrates have been shown to undergo tandem ylide formation–cycloaddition processes. The first asymmetric induction in intermolecular cycloadditions of carbonyl ylides with aryl acetylenes has been observed, with the binaphthyl catalysts giving the best enantioselectivities (up to 76% ee) and extending their usefulness.[3,12] 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.

Table 3. Enantioselective cycloadditions

Entry	Diazodione	Dipolarophile	Catalyst	Solvent	Yield[a] (%)	Ee[b] (%)	$[\alpha]_D^{T}$[c]
1	**1**	**3**	$Rh_2(R\text{-BNP})_4$	Toluene	41	10	+12.2
2	**1**	**4**	$Rh_2(R\text{-BNP})_4$	Toluene	37	38	−63.1
3	**1**	**5**	$Rh_2(R\text{-BNP})_4$	Toluene	50	31	+27.6
4	**1**	**3**	$Rh_2(S\text{-BPTV})_4$	$PhCF_3$	43	3	+2.7
5	**1**	**4**	$Rh_2(S\text{-BPTV})_4$	$PhCF_3$	47	28	+48.7
6	**1**	**5**	$Rh_2(S\text{-BPTV})_4$	$PhCF_3$	73	1	+2.0
7	**2**	**3**	$Rh_2(R\text{-BNP})_4$	Toluene	48	18	−43.8
8	**2**	**4**	$Rh_2(R\text{-BNP})_4$	Toluene	54	48	−105.5
9	**2**	**5**	$Rh_2(R\text{-BNP})_4$	Toluene	33	31	+49.0
10	**2**	**3**	$Rh_2(S\text{-BPTV})_4$	$PhCF_3$	65	40	+70.7
11	**2**	**4**	$Rh_2(S\text{-BPTV})_4$	$PhCF_3$	69	43	+97.0
12	**2**	**5**	$Rh_2(S\text{-BPTV})_4$	$PhCF_3$	72	38	+54.4

[a] Isolated yields.
[b] Ees determined by chiral HPLC using Daicel Chiralpak AD (Chiralcel OD for entries 2 and 5) column with heptane/EtOH eluant.
[c] Entries 4–6 and 10–12: $c=1$, $T=25$°C; remaining $c=0.88$–1.12, $T=20$–24°C. All in $CHCl_3$.

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References

1. (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909; (b) Karlsson, S.; Högberg, H.-E. *Org. Prep. Proced. Int.* **2001**, *33*, 105–172; (c) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50–61; (d) Kitagaki, S.; Hashimoto, S. *J. Synth. Org. Chem. Jpn* **2001**, *59*, 1157–1169; (e) Hodgson, D. M.; Stupple, P. A.; Forbes, D. C. In *Rodd's Chemistry of Carbon Compounds*, *Topical Volume*, *Asymmetric Catalysis*; Sainsbury, M., Ed.; Elsevier: Oxford, 2001; pp. 65–99; (f) Forbes, D. C.; McMills, M. C. *Curr. Org. Chem.* **2001**, *5*, 1091–1105.
2. Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett.* **1997**, *38*, 6471–6472.
3. (a) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun.* **1999**, 2185–2186; (b) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465–4476.
4. Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417–1418.
5. Donohue, A. C. University of Oxford, unpublished results.
6. Mateos, A. F.; Coca, G. P.; Alonso, J. J. P.; González, R. R.; Hernández, C. T. *Synlett* **1996**, 1134–1136.
7. Treatment of the diketone **1** (N_2=H_2) with base (in our case DBU) leads to 3-methyl-2-phenylcyclopent-2-enone, see: Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 2614–2617.
8. Iwasaki, G.; Saeki, S.; Hamana, M. *Chem. Lett.* **1986**, 173–176.
9. After commencement of our work the use of α-aryl-α-diazo ketones in Rh(II)-catalysed *oxidopyrylium* cycloadditions was reported: Padwa, A.; Precedo, L.; Semones, M. A. *J. Org. Chem.* **1999**, *64*, 4079–4088.
10. Example procedure: 1-diazo-1-phenylhexane-2,5-dione (**1**) (35 mg, 0.16 mmol) was dissolved in toluene (3 cm^3) and phenylacetylene (88 μL, 0.80 mmol) added. $Rh_2(Oac)_4$ (0.7 mg, 1 mol%) was added and the mixture stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure. Purification of the residue by column chromatography [SiO_2, 20:1 Et_2O:light petroleum (bp 40–60°C)] gave a white solid, 5-methyl-1,7-diphenyl-8-oxabicyclo[3.2.1]oct-6-en-2-one **6** (Y, Z=H) (28 mg, 60%): R_f=0.65 [1:1 light petroleum (bp 40–60°C):Et_2O]; mp 122–123°C [light petroleum (bp 40–60°C):EtOAc]; IR: ν_{max} (KBr disc)/cm^{-1}=2921 (w), 2854 (w), 1716 (s), 1448 (m), 1373 (w) and 1187 (m); ^{1}H NMR (400 MHz; $CDCl_3$): δ=7.42–7.40 (2H, m, 2×aromatic H), 7.31–7.20 (8H, m, 8×aromatic H), 6.54 (1H, s, =CH), 2.92–2.74 (2H, m, $COCH_2$), 2.43 (1H, ddd, J=13.5, 8.5 and 8.5, $COCH_2CH\mathit{H}$), 2.07 (1H, ddd, J=13.5, 8.5 and 2, $COCH_2CH\mathit{H}$) and 1.63 (3H, s, Me); ^{13}C NMR (100 MHz; $CDCl_3$): δ=203.5 (C=O), 144.0 (aromatic C), 135.4 (=CH), 135.0 (aromatic C), 132.1 (C=), 129.2 (2×aromatic CH), 128.5 (aromatic CH), 128.3 (2×aromatic CH), 128.1 (2×aromatic CH), 128.0 (aromatic CH), 126.7 (2×aromatic CH), 95.1 (Ph*C*-O), 84.5 (Me*C*-O), 35.0 (CH_2), 34.7 (CH_2) and 24.4 (Me); anal. calcd for $C_{20}H_{18}O_2$: C, 82.7; H, 6.25%. Found: C, 82.6; H, 6.25; MS (CI, NH_3): m/z (%)=308 (100) [M+NH_4^+] and 291 (35) [M+H^+] (found: [M+NH_4^+], 308.1649. $C_{20}H_{22}NO_2$ requires 308.1651).
11. Regiochemistry was confirmed by 2D NOE NMR experiments which showed a strong correlation between the methyl group and the olefinic H in each case. Aromatic π–π interactions may contribute to the origin of the regiochemistry, see: Ibata, T.; Motoyama, T.; Hamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2298–2301.
12. Hodgson, D. M.; Petroliagi, M. *Tetrahedron: Asymmetry* **2001**, *12*, 877–881.