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A Highly Enantioselective Intramolecular Heck Reaction with a Monodentate Ligand

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Since the first reports in the late 1980s the asymmetric Heck reaction (AHR) has received considerable attention. High selectivities have been reached by using bidentate ligands, usually phosphines (predominantly BINAP) or phosphine-oxazolines. A number of intermolecular AHR’s with ee’s >96% have been reported. For the intramolecular AHR, however, the ee values are typically around 80% with notable exceptions leading to ≥90% ee. The intramolecular AHR has featured a prominent role in the synthesis of complex natural products.

We have shown that phosphoramidites are versatile ligands for a variety of catalytic asymmetric transformations. Despite the fact that the classic Heck reaction was shown to occur in the presence of phosphoramidites, the use of phosphoramidites as chiral ligands in an AHR resulted in very low enantioselectivity. We designed prochiral cyclohexadienone 1 as a new substrate for the intramolecular AHR (see Figure 1). Upon AHR, the stereogenic center is not created at the site of C–C bond formation, but instead the cyclohexadienone is desymmetrized. We expected the chiral catalyst to show high face-selectivity (based on the excellent face-selectivity already observed in asymmetric 1,4-additions to cyclohexadienones) leading to 4a-methoxy-4a-benzo[c]chromen-2(6H)-one, which could act as a model compound for, e.g., the synthesis of the anticancer Amaryllidaceae alkaloid pancratistatin.

Herein we report cyclohexadienones as new substrates for the intramolecular AHR and the remarkable finding that monodentate phosphoramidites are effective ligands for this highly enantioselective AHR with ee’s up to 96%.

Cyclohexadienone 1 is efficiently synthesized in two steps from commercially available 2-iodobenzyl chloride 3. Formation of the monoether of hydroquinone in 91%, using benzyl chloride 3, is followed by phenolic oxidation with phenyliododiacetate (PIDA) in MeOH to provide 1 in 83% yield. (Scheme 1)

Since, to the best of our knowledge, all successful ligands used so far for the AHR were bidentate, we focused our initial studies on the use of bidentate TADDOL-based phosphoramidite L*-1 as chiral ligand. Employing an in situ prepared catalyst from Pd(OAc)₂ and L*-1 (1:2 ratio) in the presence of K₂CO₃ as a base in THF we indeed obtained full conversion of the starting material product 2 in 68% ee (Table 1). Changing the solvent to CHCl₃ resulted in full conversion and 86% ee. For NMP and DMA, commonly used solvents in Heck couplings, the stereoselectivities were much lower (ee <60%), whereas for acetonitrile and DMSO racemic product was obtained due to a very fast background reaction (not involving L*).

As is commonly seen in AHR’s, the nature of the base has a dramatic effect on the reaction (entries 6–10). The use of Et₃N resulted in a slower reaction but with enhanced selectivity. The best results were obtained with iPr₂EtN and especially Cy₂MeN (based on recent reports of the effectivness of this bulky tertiary amine), both with full conversion and high enantioselectivities of 89% and 90%, respectively. Additives such as nBu₄NX (X = I, OTf) or iPr₂EtN·HCl did not result in improvement of the reaction, whereas with silver salts no conversion was obtained. This AHR turned out not to be very sensitive to air and water and it could even be performed with nondistilled solvents.

Recent developments in asymmetric catalysis show that high enantioselectivities can be induced by monodentate chiral ligands and that monodentate BINOL based phosphoramidites are excellent ligands for rhodium-catalyzed asymmetric hydrogenations. Although monodentate ligands were never very successful in inter- as well as intramolecular AHR’s, we examined the monodentate analogue L*-2 of bidentate ligand L*-1 in the Heck coupling of 1.

Much to our delight the use of monodentate ligand L*-2 resulted in a more selective conversion of 1 to 2 compared to the Heck coupling of 1 employing bidentate ligand L*-2 (entries 15,16). Again Cy₂MeN is the base of choice. With use of Pd(OAc)₂ in the presence of L*-2 and Cy₂MeN, full conversion was reached, providing 2 in 71% isolated yield with an excellent ee of 96%, without the use of expensive silver or toxic thallium salts.
ligands and not requiring any additives, has been developed. Excellent enantioselectivities up to 96% ee are reached for the first time in a Heck reaction with monodentate ligands. Extension of the scope of this reaction and detailed mechanistic studies are currently in progress.

Acknowledgment. We thank Mr. M. B. van Gelder for carrying out the HPLC measurements. Financial support from the Dutch Foundation for Scientific Research (NWO-CW) is gratefully acknowledged.

Supporting Information Available: Experimental and chromatographic details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References
(9) The AHR of a cyclohexadiene-alcohol has been reported previously; Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. Tetrahedron Lett. 1993, 34, 4219.
(12) For a review of phenolic oxidations with PIDA, see: Pelter, A.; Internet at http://pubs.acs.org.
(15) This is the average of 8 experiments with ee’s ranging from 94 to 96.5%.
(16) The results of the AHR of two other examples of dienes, resulting in 93% and 75% ee, respectively, are given in the Supporting Information.
(22) The ligand-to-palladium ratio in the actual catalytically active complex is at present unclear.

Table 1. AHR of 1 to 2, Using Phosphoramidites as Ligand

<table>
<thead>
<tr>
<th>entry</th>
<th>L* solvent</th>
<th>base</th>
<th>additive</th>
<th>conv. (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1 L*1</td>
<td>THF</td>
<td>K$_2$CO$_3$</td>
<td></td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>2 L*1</td>
<td>CH$_2$Cl$_2$</td>
<td>K$_2$CO$_3$</td>
<td></td>
<td>100</td>
<td>84</td>
</tr>
<tr>
<td>3 L*1</td>
<td>CHCl$_3$</td>
<td>K$_2$CO$_3$</td>
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<td>100</td>
<td>86</td>
</tr>
<tr>
<td>4 L*1</td>
<td>Toluene</td>
<td>K$_2$CO$_3$</td>
<td></td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>5 L*1</td>
<td>CHCl$_3$</td>
<td>PS$^d$</td>
<td>&lt;10</td>
<td></td>
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</tr>
<tr>
<td>6 L*1</td>
<td>CHCl$_3$</td>
<td>K$_2$PO$_4$</td>
<td></td>
<td>60</td>
<td>86</td>
</tr>
<tr>
<td>7 L*1</td>
<td>CHCl$_3$</td>
<td>PMP</td>
<td>68</td>
<td>87</td>
<td></td>
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<tr>
<td>8 L*1</td>
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<td>Et$_3$N</td>
<td>35</td>
<td>92</td>
<td></td>
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<tr>
<td>9 L*1</td>
<td>CHCl$_3$</td>
<td>iPr$_3$EN</td>
<td>100</td>
<td>89</td>
<td></td>
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<tr>
<td>10 L*1</td>
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<td>Cy$_2$MeN</td>
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<td>90</td>
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<tr>
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<td>iPr$_3$EN</td>
<td>iPr$_3$EN$+$HCl</td>
<td>80</td>
<td>83</td>
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<tr>
<td>12 L*1</td>
<td>CHCl$_3$</td>
<td>iPr$_3$EN</td>
<td>e</td>
<td>95</td>
<td>75</td>
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<tr>
<td>13 L*1</td>
<td>CHCl$_3$</td>
<td>iPr$_3$EN</td>
<td>f</td>
<td>90</td>
<td>78</td>
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<tr>
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<td>iPr$_3$EN</td>
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<td>$&lt;$2</td>
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<tr>
<td>15 L*1</td>
<td>CHCl$_3$</td>
<td>iPr$_3$EN</td>
<td></td>
<td>100</td>
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<td>CHCl$_3$</td>
<td>Cy$_2$MeN</td>
<td></td>
<td>100</td>
<td>96</td>
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</tbody>
</table>

$^a$ Reaction conditions: 0.3 mmol of diene 1, 6 mol % of Pd(OAc)$_2$, 12 mol % of ligand, 4 equiv of base, 3 mL of solvent, 1 equiv of additive, reflux, 2 days. $^b$ Determined by $^1$H NMR, isolated yields at 100% conversion 70–75%. $^c$ Determined by HPLC analysis using a DAICEL OD or AS column. $^d$ Proton Sponge. $^*nu$Bu$_4$NI, $^*nu$BuNOT.

Scheme 2. Proposed Catalytic Cycle

For comparison, BINAP was also examined as a chiral ligand, using our optimized conditions or the Shibasaki or Overman conditions, and product 2 was obtained after 48 h in 0–50% yield and 0–5% ee.

On the basis of extensive mechanistic studies of Heck couplings, the formation of 2 can be rationalized as shown in Scheme 2. Initially, a chiral Pd(0) complex A is formed. Oxidative addition of diene 1 results in Pd(II) complex B. Subsequent C–C bond formation (association and insertion into Pd–C) leads to complex C, which does not have a syn β-hydride. To reach the final product 2 epimerization of the C-2 center leading to D followed by syn β-hydride elimination to complex E needs to take place. The net trans elimination can be explained via a mechanism involving oxo-α,α′-allylpalladium intermediates, similar to enolization in normal ketones, which have found precedence in the Pd-catalyzed dehydroxylation of silyl enol ethers. It should be noted that several examples of apparent trans β-hydride elimination have appeared in the literature. Finally, reductive elimination of HI with base leads to the starting complex A. Preliminary mechanistic studies indicate a possible neutral pathway.

In conclusion, an efficient enantioselective intramolecular Heck reaction of cyclohexadienones, using readily available and modular TADDOL-based mono- and bidentate phosphoramidites as chiral