Asymmetric Catalysis

DOI: 10.1002/anie.201104595

Catalytic Asymmetric Intramolecular Hydroacylation with Rhodium/Phosphoramidite–Alkene Ligand Complexes**

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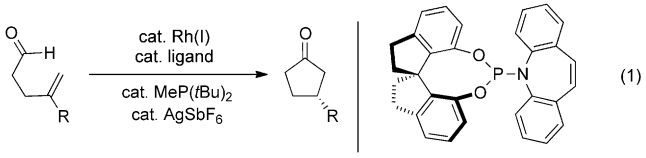
The rational design and development of novel transition-metal catalysts bearing diolefin[1,2] and phosphine–olefin ligands[3] has recently gained attention for the promotion of catalytic enantioselective reactions such as conjugate and imine additions, as well as the cyclization of ynals.[4] The heteroleptic complexes generated from phosphine–alkene ligands can be particularly useful as they include at least two donors with distinct steric and electronic properties. Phosphine–alkene ligands featuring dibenzo[*b*,*f*]azepine[5] motifs have previously been reported in enantioselective allylic displacement[3j,6] and conjugate addition[7] reactions. As the exploration of these and related ligand types continues to evolve, their use in novel processes will increase. Herein, we report an asymmetric intramolecular Rh-catalyzed hydroacylation[8] reaction of pent-4-enals for the preparation of cyclopentanones [Eq. (1)]. Two key features of the catalytic system are noteworthy: this is the first time phosphoramidite–



(1)

alkene ligands have been used for this reaction type and the incorporation of an achiral phosphine coligand is necessary to promote enantioselective catalysis.

After the seminal report in 1972[9] by Sakai et al., in which stoichiometric Rh^I was used, Miller and co-workers[10] and Larock et al.[11] showed that substituted γ-pentenals undergo hydroacylative cycloisomerization using $[Rh(PPh_3)_3Cl]$. Their protocol featured solvent saturated with ethylene and necessitated high catalyst loading (up to 50 mol%); additionally, they noted the formation of considerable amounts of side products from competitive decarbonylation pathways. Bosnich and co-workers[12] and Sakai et al.[13] independently reported catalytic enantioselective intramolecular hydroacylation with cationic rhodium perchlorate catalysts prepared from binap or Me-DuPhos.[14] These studies showed that to obtain good product selectivity the matching of the diphosphine ligand to the pentenal substrates was of the utmost importance. Subsequent investigations with isotopic labelling have also been undertaken to shed light on the mechanistic details.[10,15] It has been suggested that the benefits of ethylene in the reaction mixture, mentioned in the early reports, arise from the formation of a coordinatively saturated cationic rhodium species stabilized against decomposition.[10,11] This aspect of using ethylene piqued our interest and led us to examine the use of donor ligands incorporating an olefin. Additionally, we envisioned the implementation of combinatorial catalysis[16] involving heteroleptic complexes generated in situ, an approach that is highly rewarding as illustrated by the observations of Reetz et al.,[17] Shibasaki and co-workers,[18] and Ding and co-workers.[19]

In prospecting experiments we examined pentenal **1a**, as the prototypical substrate, under various reaction conditions with complexes generated in situ from $[\{RhCl(C_2H_4)_2\}_2]$ and phosphoramidite ligands (*S*)-**L1**[6] and (*R*,*R*,*R*)-**L2**[20] in the presence of Ag^I (Table 1). These reaction conditions failed to provide cyclopentanone. Interestingly, the introduction of Ph_3P (8 mol%) into the reaction mixture, which included (*S*)-**L1** (8 mol%), $[\{Rh(C_2H_4)_2\}]$ (4 mol%), and $AgSbF_6$ (8 mol%), led to formation of **2a** in 52% yield and 66% *ee* (Table 1, entry 3).[21] This result from a reaction involving the addition of an achiral ligand is intriguing and was unexpected. The inclusion of a second equivalent of PPh_3, relative to (*S*)-**L1**, slowed the reaction and resulted in lower enantioselectivity (21% yield, 40% *ee*; Table 1, entry 4). When ligand **L2** was tried under similar reaction conditions no product was observed (Table 1, entry 5). After the initial results with ligand (*S*)-**L1**, the addition of several phosphine coligands was investigated.[22] The use of P(2-furyl)$_3$ shut down catalysis altogether (Table 1, entry 6) and $AsPh_3$ did not promote the reaction efficiently (18% yield, 64% *ee*; Table 1, entry 7). Furthermore, employing $P(C_6F_5)_3$ provided **2a** in high selectivity, albeit in poor yields (20% yield, 90% *ee*; Table 1, entry 8) and attempts with P(*o*-tol)$_3$ (44% yield, 64% *ee*, Table 1, entry 9) and P(2,6-OMePh)$_3$ (36% yield, 80% *ee*; Table 1, entry 10) were unsuccessful in improving upon the initial result. Additionally, alkyl-substituted phosphine ligands $MePPh_2$ (40% yield, 66% *ee*; Table 1, entry 11) and PCy_3 (60% yield, 50% *ee*; Table 1, entry 12) only gave **2a** with modest yields and selectivity. However, the use of the bulky, electron-rich P(*t*Bu)$_3$ greatly increased the reaction selectivity (94% *ee*; Table 1, entry 13); when the less bulky MeP(*t*Bu)$_2$ was investigated, both the reaction yield and selectivity were improved (78% yield, 95% *ee*; Table 1, entry 14). As a control, the use of (*S*)-**L3**, which lacks the olefin donor, had a negative impact on the reaction performance (33% yield, 64% *ee*; Table 1, entry 15). Additionally, the use of P(*t*Bu)$_3$ (25% conversion, 34% *ee*; Table 1,

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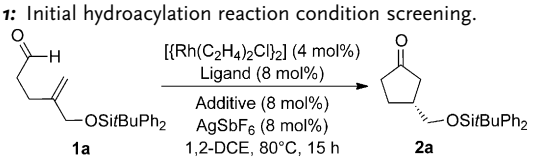
[**] We thank Dr. Marc LaFrance for his assistance in ligand synthesis.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104595.

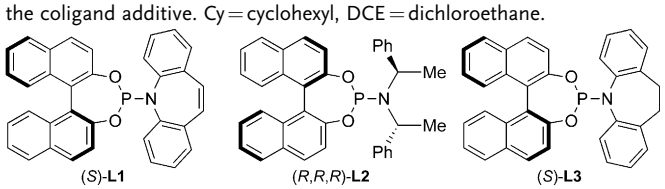
Table 1: Initial hydroacylation reaction condition screening.



1a **2a**

Entry	Ligand	Additive	Conv.[%][a]	Yield [%]	*ee* [%][b]
1[c]	(*S*)-**L1**	None	–[d]	–	–
2[c]	(*R*,*R*,*R*)-**L2**	None	–[d]	–	–
3	(*S*)-**L1**	PPh_3	>95	52	66
4[e]	(*S*)-**L1**	PPh_3	36	21	40
5	(*R*,*R*,*R*)-**L2**	PPh_3	–[d]	–	–
6	(*S*)-**L1**	$P(2\text{-furyl})_3$	–[d]	–	–
7	(*S*)-**L1**	$AsPh_3$	>95	18	64
8	(*S*)-**L1**	$P(C_6F_5)_3$	>95	20	90
9	(*S*)-**L1**	$P(o\text{-tol})_3$	>95	44	64
10	(*S*)-**L1**	$P(2,6\text{-OMePh})_3$	75	36	80
11	(*S*)-**L1**	$MePPh_2$	>95	40	66
12	(*S*)-**L1**	PCy_3	>95	60	50
13	(*S*)-**L1**	$P(t\text{Bu})_3$	80	58	94
14	(*S*)-**L1**	$MeP(t\text{Bu})_2$	>95	78	95
15	(*S*)-**L3**	$MeP(t\text{Bu})_2$	63	33	64
16	(*S*)-**L3**	$P(t\text{Bu})_3$	25	–	34
17[e]	(*S*)-**L3**	$PMe(t\text{Bu})_3$	16	–	66

[a] Conversion was determined by ^{1}H NMR spectroscopy. [b] The *ee* value was measured by supercritical fluid chromatography (SFC) analysis (Chiralpak OJ-H). [c] Also performed using 16 mol% of ligand. [d] No reaction occured. [e] Reaction was carried out using 16 mol% of the coligand additive. Cy = cyclohexyl, DCE = dichloroethane.

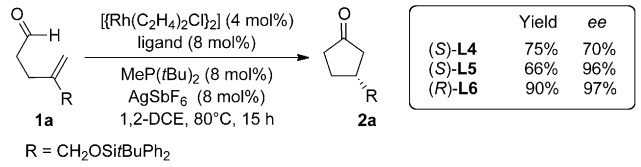


(*S*)-**L1** (*R*,*R*,*R*)-**L2** (*S*)-**L3**

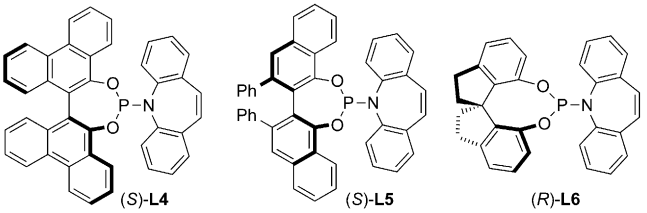
entry 16) or 16 mol% of $MeP(t\text{Bu})_2$ (16% conversion, 66% *ee*; Table 1, entry 17) in combination with (*S*)-**L3** failed to improve the process.

A novel set of phosphine–alkene ligands ((*S*)-**L4**, (*S*)-**L5**, and (*R*)-**L6**) featuring three distinct chiral constructs was prepared and then examined. This study commenced with phenanthrol-based (*S*)-**L4** but use of the resulting complex gave only a modest outcome for **2a** (75% yield, 70% *ee*; Scheme 1). The vanol-derived ligand (*S*)-**L5** led to the product **2a** but only slightly improved the selectivity (66% yield, 96% *ee*; Scheme 1) However, the spinol-derived[23] ligand (*R*)-**L6** gave the best outcome, as **2a** was isolated in 90% yield and 97% *ee* (Scheme 1).[24]

It is worthwhile to provide a context for the development of an approach to β-substituted cyclopentanones by hydroacylation, because conjugate addition approaches for their preparation in high optical activity and yield have been reported. However, alkyl-substituted cyclopentanones, other than those incorporating the most rudimentary of substituents, are not always easily accessed. Moreover, conjugate additions require the stoichiometric use of metal organic reagents (that is, Grignard,[25] as well as organotin,[26] zinc,[27] aluminium,[28] lithium,[29] and copper[30] species), or metalloid reagents (that is, organoboron,[31] and organosilicon[32]), the



	Yield	*ee*
(*S*)-**L4**	75%	70%
(*S*)-**L5**	66%	96%
(*R*)-**L6**	90%	97%



(*S*)-**L4** (*S*)-**L5** (*R*)-**L6**

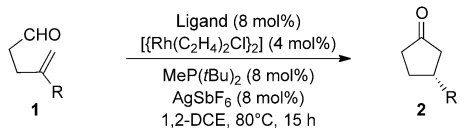
Scheme 1. Phosphoramidite–alkene ligand screening.

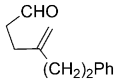
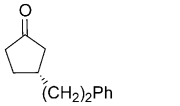
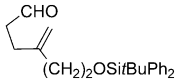
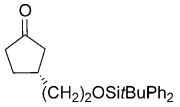
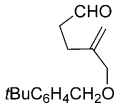
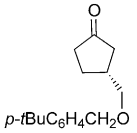
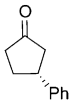
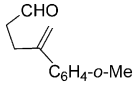
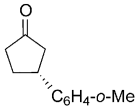
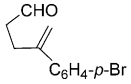
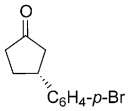
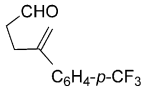
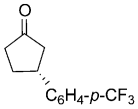
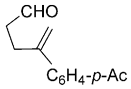
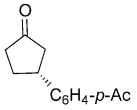
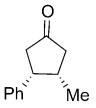
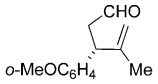
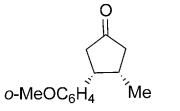
preparation of which may be cumbersome and produce waste. By contrast, hydroacylations may be considered ideal[33] in so far as all of the atoms of the starting material are found in the product.

With the optimized reaction conditions established, a series of pent-4-enal substrates was prepared and examined. Alkyl-functionalized pent-4-enals (**1b–d**) were studied first, and they cleanly provided cyclopentanone products **2b** (72% yield, 95% *ee*; Table 2, entry 1), **2c** (80% yield, 92% *ee*; Table 2, entry 2), and **2d** (75% yield, 96% *ee*; Table 2, entry 3) in good yield and excellent selectivity. Next, a series of aryl-substituted pentenals were examined beginning with electron-rich aryl substrates **1e** and **1f**, which furnished the cyclized products **2e** (62% yield, 96% *ee*; Table 2, entry 4) and **2f** (54% yield, 90% *ee*; Table 2, entry 5), respectively. Pentenal systems with electron-poor aryl rings substituted with halogen (**1g**), trifluoromethyl (**1h**), and carbonyl (**1i**) groups provided products **2g** (56% yield, 90% *ee*; Table 2, entry 6), **2h** (68% yield, 97% *ee*; Table 2, entry 7), and **2i** (54% yield, 90% *ee*; Table 2, entry 8), in high optical purity. Interestingly, we observed that when the alkyl and aryl pentenal substrates were submitted to identical reaction conditions, the configuration of the cyclopentanones isolated is opposite for β-alkyl- and β-aryl-substituted products. When the hydroacylation method was applied to the 3-substituted pent-4-enal substrate (3*R*)-**1j** using (*S*)-**L6** ligand, the *syn*-hydroacylated product **2j** was readily obtained (68% yield, 80% *ee*, *syn*/*anti* = 98:2; Table 2, entry 9). Indeed, a similar outcome was observed for (3*R*)-**1k**, as cyclopentanone **2k** was isolated in good yield and diastereoselectivity (65% yield, 90% *ee*, *syn*/*anti* = 94:6; Table 2, entry 10).

In summary, we have shown that cationic rhodium complexes featuring novel phosphoramidite–alkene ligands and an achiral phosphine coligand effectively catalyze the intramolecular hydroacylation of pent-4-enal substrates, thus providing β-substituted cyclopentanones, which incorporate alkyl and arene groups, in good yield and excellent selectivity. This report represents an expansion of the types of reactions using phosphoramidite–olefin ligands. The fact that the reactivity of the complexes derived from phospine–alkene ligands can be modulated or fine-tuned by the addition of a second achiral phosphine may provide additional avenues for further developments involving olefins as ligands.

Table 2: Pent-4-enal substrate scope.[a]



Entry	Pentenal		Ligand	Product		Yield [%]	*ee* [%][b]
1		**1b**	(*R*)-**L6**		**2b**	72	95
2		**1c**	(*R*)-**L6**		**2c**	80	92
3		**1d**	(*R*)-**L6**		**2d**	75	96
4		**1e**	(*S*)-**L6**		**2e**	62	96
5		**1f**	(*S*)-**L6**		**2f**	54	90
6		**1g**	(*S*)-**L6**		**2g**	56	90
7		**1h**	(*S*)-**L6**		**2h**	68	97
8		**1i**	(*S*)-**L6**		**2i**	54	90
9[c]		**1j** (80% *ee*)	(*S*)-**L6**		**2j**	68	80 (98:2)[d]
10[c]		**1k** (90% *ee*)	(*S*)-**L6**		**2k**	65	90 (94:6)[d]

[a] Reaction conditions: pent-4-enal **1** (0.16 mmol), [{RhCl(C_2H_4)$_2$}$_2$] (4.0 mol%), ligand (8 mol%), MeP(*t*Bu)$_2$ (8 mol%), $AgSbF_6$ (8 mol%), 1,2-DCE (0.1 M), 80°C, 15 h. [b] The *ee* value was measured by supercritical fluid chromatography (SFC) analysis. [c] Reaction time was 5 h. [d] The d.r. (*syn*/*anti*) is in brackets.

Experimental Section

(*R*)-**L6** (6.1 mg, 13 μmol) and then 0.20 mL of CH_2Cl_2 were added to a flask charged with [{RhCl(C_2H_4)$_2$}$_2$] (2.5 mg, 6.4 μmol) under Ar. After 10 min MeP(*t*Bu)$_2$ (2.06 mg, 13 μmol) was added as a CH_2Cl solution (0.20 mL) followed by $AgSbF_6$ (4.4 mg, 13 μmol) in 1,2-DCE (0.20 mL). The resultant deep-red solution was stirred in the dark overnight and the grey precipitate that formed (AgCl) was removed via syringe filtration and rinsed with 1 mL 1,2-DCE. The resulting solution was introduced to a new flask containing pent-4-enal **1a** (57 mg, 0.16 mmol) and heated at 80°C for 15 h. Upon completion, the reaction mixture was cooled to 23°C, diluted with Et_2O, and filtered through a pad of silica gel. Removal of the solvent under reduced pressure followed by purification of the residue by column chromatography on silica gel (*n*-pentane/Et_2O; 95:5) gave **2a** (51 mg, 90% yield, 97% *ee*) as a clear oil.

Received: July 4, 2011
Published online: September 16, 2011

Keywords: asymmetric catalysis · cyclopentanone · hydroacylation · P ligands · rhodium

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