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Borrowing hydrogen in an indirect asymmetric Wittig reaction

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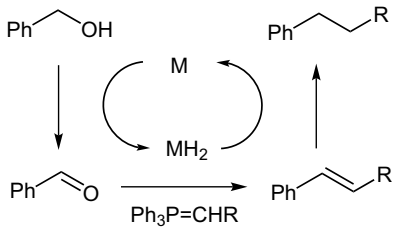
Abstract—An asymmetric C–C bond formation has been achieved by iridium-catalysed coupling of benzyl alcohol with a phosphonium ylide using a borrowing hydrogen strategy.

1. Introduction

We have been developing an indirect Wittig reaction on alcohols using iridium[1] and ruthenium[2] complexes which proceeds via the route shown in Scheme 1. The metal catalyst 'borrows hydrogen' from an alcohol to generate an aldehyde which then undergoes a Wittig reaction to form an alkene. The hydrogen is then returned to provide an overall alkylation process.



Scheme 1. Borrowing hydrogen in an indirect Wittig reaction.

Similar approaches have been reported involving the conversion of the intermediate aldehyde into an alkene via aldol and related condensation reactions.[3,4]

2. Results and discussion

For an asymmetric variant of the indirect Wittig reaction, the enantioselective step will be the addition of hydrogen to the intermediate alkene. Whilst the metal-catalysed asymmetric reduction of alkenes by direct hydrogenation is very well-known,[5] the related process using an alcohol as the hydrogen donor has received little attention.[6] We therefore chose to screen the asymmetric reduction of prochiral alkene **1** using isopropanol as a model for the asymmetric step of an indirect Wittig reaction. This particular prochiral alkene was chosen because the combination of a primary benzylic alcohol with a stabilised phosphonium ylide is known to be effective in the achiral process.[1,2] Additionally, the alkene-forming step from PhCHO and $Ph_3P{=}C(Me)CO_2Et$ is known to be highly (*E*)-selective,[7] thus reducing the possibility of compromising the enantioselectivity of the reaction by the reduction of a mixture of alkene isomers.

The reduction of alkene **1** by isopropanol was performed using an Anachem RS12 48-position stem block and Gilson 215 autosampler, using ligands **3**–**11** (Fig. 1) with catalyst precursors **12**–**14** (Fig. 2). In addition, the commercially available complexes **15**–**17** (Fig. 3) were screened for activity (Scheme 2). Reactions were performed in toluene, diglyme, DMSO and DMF.

Initially the reactions were analysed for conversion to product by HPLC. Samples with a reasonable level of conversion were then further analysed by chiral HPLC to establish the level of asymmetric induction obtained in the reaction.[8] These results are presented in Table 1.

From the results in Table 1, it was clear that from the reactions screened, the combination of BINAP **5** and the iridium catalyst **14** was the most suitable for further development. Many of the reactions involving the ruthenium

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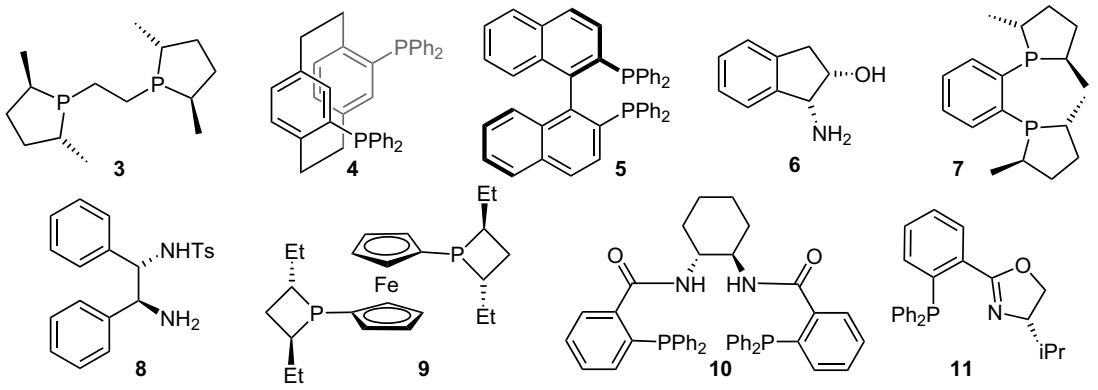


Figure 1. Ligands screened in the asymmetric transfer hydrogenation of alkene **1**.

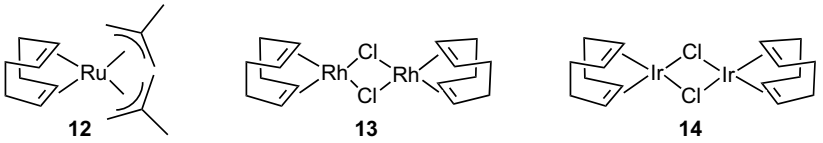


Figure 2. Catalyst precursors screened in the asymmetric transfer hydrogenation of alkene **1**.

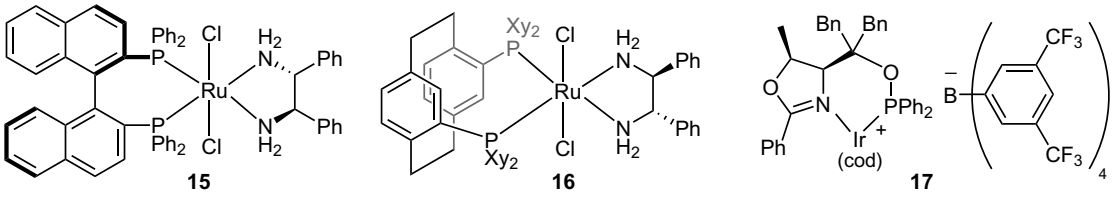
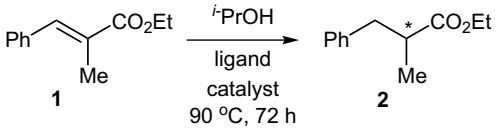


Figure 3. Pre-formed complexes screened in the asymmetric transfer hydrogenation of alkene **1**.



Scheme 2. Reduction of prochiral alkene **1** by transfer hydrogenation.

catalyst **12** provided good conversions into product, but the highest enantioselectivity was a modest 31% ee. None of the reactions involving the rhodium catalyst **13** gave sufficient conversion to warrant examination of the enantioselectivity. The reaction of benzyl alcohol **18** with phosphonium ylide **19** was then investigated using the iridium/BINAP catalytic system (Scheme 3).

Table 1. Reduction of alkene **1** by metal-catalysed transfer hydrogenation

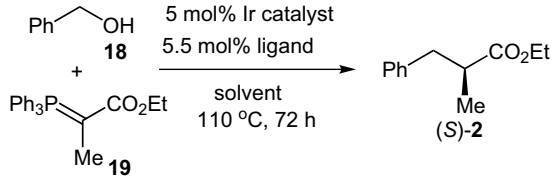
Entry	Metal	Ligand	Toluene conversion (%); ee (%)	Diglyme conversion (%); ee (%)	DMSO conversion (%); ee (%)	DMF conversion (%); ee (%)
1	Ru (**12**)	**3**	85; 11	100; 12	17; 1	97; 6
2	Ru (**12**)	**4**	42; 23	53; 19	2; —	55; 18
3	Ru (**12**)	**5**	13; 30	16; 7	0; —	28; 1
4	Ru (**12**)	**6**	13; 9	10; —	0; —	35; 8
5	Ru (**12**)	**7**	57; 31	89; 3	12; 1	57; 8
6	Ru (**12**)	**8**	8; —	9; —	0; —	12; —
7	Ru (**12**)	**9**	62; 11	55; 7	4; —	43; 11
8	Ru (**12**)	**10**	33; 5	21; 3	24; —	57; 10
9	Ru (**12**)	**11**	22; 1	31; 3	3; —	60; 3
10	Rh (**13**)	**3**	2; —	2; —	2; —	2; —
11	Rh (**13**)	**4**	4; —	2; —	3; —	1; —
12	Rh (**13**)	**5**	0; —	2; —	2; —	0; —
13	Rh (**13**)	**6**	0; —	0; —	3; —	0; —
14	Rh (**13**)	**7**	1; —	2; —	3; —	0; —
15	Rh (**13**)	**8**	0; —	1; —	0; —	0; —
16	Rh (**13**)	**9**	2; —	0; —	2; —	0; —
17	Rh (**13**)	**10**	2; —	16; —	0; —	0; —
18	Rh (**13**)	**11**	3; —	1; —	3; —	0; —
19	Ir (**14**)	**3**	40; 10	16; 6	3; —	19; 1

Table 1 (*continued*)

Entry	Metal	Ligand	Toluene conversion (%); ee (%)	Diglyme conversion (%); ee (%)	DMSO conversion (%); ee (%)	DMF conversion (%); ee (%)
20	Ir (**14**)	**4**	25; 1	27; 6	0; —	17; 6
21	Ir (**14**)	**5**	**85; 57**	**46; 55**	**22; 67**	**100; 66**
22	Ir (**14**)	**6**	0; —	4; —	2; —	3; —
23	Ir (**14**)	**7**	79; 15	81; 12	4; —	52; 10
24	Ir (**14**)	**8**	2; —	3; —	5; —	0; —
25	Ir (**14**)	**9**	55; 9	31; 6	13; 0	64; 16
26	Ir (**14**)	**10**	7; —	8; —	11; —	8; —
27	Ir (**14**)	**11**	5; —	4; —	14; —	5; —
28	Complex **15**		7; —	3; —	0; —	6; —
29	Complex **16**		1; —	2; —	0; —	11; 0
30	Complex **17**		11; 0	37; 0	7; —	16; 0

We were pleased to find that the enantiomeric excess in these reactions was marginally higher than for the simple alkene reduction. The solvent, catalyst and ligand were varied, as shown in Table 2. Toluene was found to provide a higher enantiomeric excess than either DMF or DMSO. The use of (*R*)-TolBINAP and (*R*)-XylylBINAP slightly compromised both the conversion and the enantiomeric excess. The cationic iridium catalyst $(cod)_2IrBF_4$ essentially afforded racemic product, whilst the use of Cp^*IrCl_2 provided a slightly improved enantiomeric excess, but with lower conversion.

The reaction was performed on a 2 mmol scale under argon and rigorously anhydrous and anaerobic conditions, which provided a further increase in the enantioselectivity of the reaction (Scheme 4).[9] The isolated product was examined by polarimetry and by comparison with the literature assigned as the (*R*)-enantiomer when (*S*)-BINAP was used as the ligand.[10]

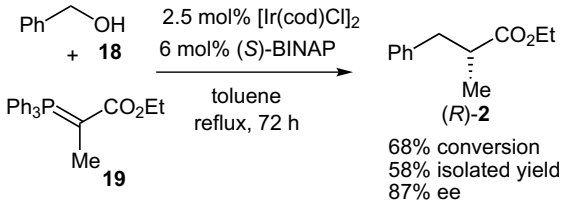


Scheme 3. Asymmetric C–C bond formation from benzyl alcohol.

Table 2. Iridium/ligand combinations employed

Solvent	Catalyst/ligand[a]	Conv (%)	ee (%)
PhMe	$[Ir(cod)Cl]_2$/(*R*)-BINAP	60	81
DMF	$[Ir(cod)Cl]_2$/(*R*)-BINAP	58	77
DMSO	$[Ir(cod)Cl]_2$/(*R*)-BINAP	58	69
PhMe	$[Ir(cod)Cl]_2$/(*R*)-TolBINAP	56	65
PhMe	$[Ir(cod)Cl]_2$/(*R*)-XylylBINAP	48	74
PhMe	$[Ir(coe)_2Cl]_2$/(*R*)-BINAP	47	66
PhMe	$(cod)_2IrBF_4$/(*R*)-BINAP	55	1
PhMe	Cp^*IrCl_2/(*R*)-BINAP	52	83

[a] 5 mol % in Ir, 5.5 mol % in ligand.



Scheme 4. Optimised conditions for the asymmetric process.

3. Conclusion

In conclusion, we have reported the first example of an asymmetric indirect Wittig reaction on an alcohol.

Acknowledgements

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8. HPLC conditions used were Chiralcel OJ, hexane (100%), 1 mL/min, 14.83 min (*S*), 15.39 min (*R*).
9. *Experimental procedure*: Commercially available (carboxyethylidene)triphenylphosphorane (870 mg, 2.4 mmol), $[Ir(cod)Cl]_2$ (33.6 mg, 2.5 mol %; 5 mol % in Ir) and (*S*)-BINAP (74.7 mg, 6 mol %) were charged to a Young's tap carousel tube and purged with argon. Benzyl alcohol (216 mg, 2.0 mmol) and dry toluene (2 mL) were added under a flow of argon. The tap was closed and the reaction heated at reflux for 72 h. Removal of toluene in vacuo and an analysis of the NMR of the crude material indicated 68% conversion. Purification by column chromatography (silica; petroleum ether/ether 19:1) gave a (*R*)-2 as a colourless liquid (223 mg, 58%). NMR data was consistent with the literature.[10] Enantiomeric excess was determined by chiral HPLC.[8]
10. Colwell, A. R.; Duckwell, L. R.; Brooks, R.; McManus, S. P. *J. Org. Chem.* **1981**, *46*, 3097–3102, which reports; $[\alpha]_D^{22.2} = +15.0$ (*c* 2.836, EtOH) for (*S*)-2. The compound isolated from Scheme 4 gave; $[\alpha]_D^{21} = -13.7$ (*c* 2.85, EtOH).