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Rhodium catalysed tandem conjugate addition-protonation: an enantioselective synthesis of 2-substituted succinic esters†

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The rhodium catalysed addition of potassium trifluoro(organo-)borates to dimethyl itaconate generates an intermediate complex which on protonation provides enantioenriched succinic esters.

The rhodium catalysed asymmetric addition of aryl and alkenyl organoboron reagents to activated alkenes has emerged as fundamental methodology for organic synthesis.[1] The reaction can be carried out in aqueous solvent and affords excellent enantioselectivities (> 90% ee) across a wide range of substrates. Interestingly, there are limited reports of α-substituted activated alkenes being employed as substrates.[2] This can be attributed to their lower reactivity and crucially, in the asymmetric process the enantioselectivity is determined at the hydrolysis step of an oxa-π-allylrhodium intermediate and not at the insertion step (Fig. 1).[3]

In previous reports, we and others, have revealed enantioselective rhodium catalysed additions of organoboranes to α,β-dehydroamino acid derivatives allowing access to a wide range of substituted phenylalanine α-amino acids (Y = NHAc, Fig. 1).[4] In this paper we wish to present preliminary results in the first enantioselective synthesis of 2-substituted succinic esters by a tandem rhodium catalysed conjugate addition–enantioselective protonation.[5]

A preliminary investigation into the tandem 1,4-addition–enantioselective protonation by the addition of naphthyl or phenylboronic acid to dimethyl itaconate (**1**) in the presence of $Rh(acac)(C_2H_2)_2$, (*R*)-BINAP and dioxane : water (10 : 1) as the solvent/proton source, afforded high yields of product **3a** (70–90%) but low enantioselectivity (< 5% ee). In spite of prolonged attempts to optimise this process by changing or increasing the amount of ligand and other reaction parameters (solvent, temperature, rhodium complex), we were not successful in improving the enantioselectivity.[6] It had been reported that potassium trifluoro(organo)borate salts, which are easily prepared from the corresponding boronic acid, offer practical advantages in terms of reactivity and stability for rhodium catalysed conjugate addition reactions.[7] Our initial experiments confirmed that the addition of **2a** to **1** was promoted by complexes formed from cationic rhodium salts, with complexes formed from neutral species such as $Rh(acac)(C_2H_4)_2$ failing to efficiently catalyse the reaction. Interestingly, we noted that additional chiral ligand was essential to achieve good asymmetric induction with either pre-formed complexes or those prepared *in situ* (Scheme 1).[8] It is feasible that the pre-formed rhodium–BINAP complex decomposes to an active but achiral catalyst in the absence of extra ligand, however this does not occur with simpler substrates under similar conditions. The excess ligand could effect the enantioselective protonation by blocking free coordination sites on rhodium or possibly suppressing facial isomerisation of the oxa-π-allyl intermediate.[9] Further studies are under way to determine the composition of the enantioselective catalyst.

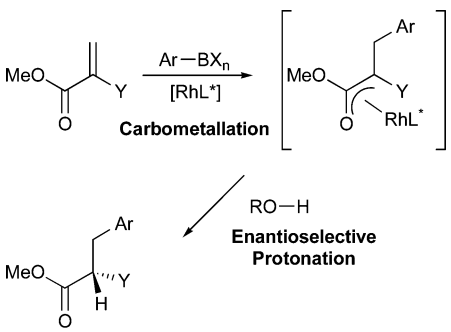
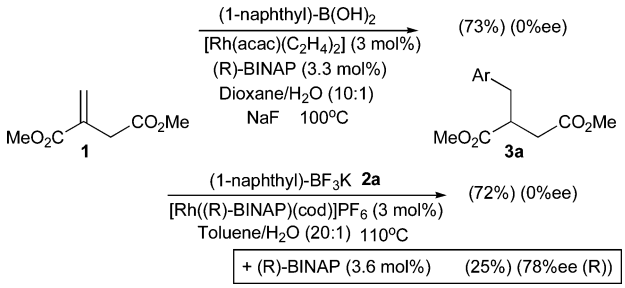
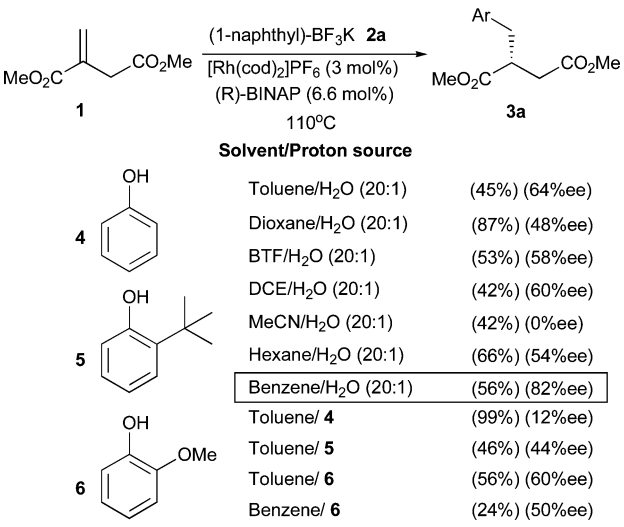


Fig. 1 Enantioselectivity controlled by protonation.

The enantioselectivity proved to be highly dependent on the solvent system (Scheme 2). For convenience we performed the addition of trifluoro(organo)borate salts to dimethyl itaconate (**1**) in the presence of a cationic rhodium complex prepared *in situ* from $[Rh(cod)_2][PF_6]$ and (*R*)-BINAP in a solvent–water mix (20 : 1) at 110 °C as described by Darses and Genêt for the addition to 2-cyclohexenone but with additional ligand (2.2 equiv.).[10] It is useful to note that the use of benzene as solvent resulted in a significant enhancement of enantioselectivity compared to toluene and dioxane, the usual solvents of choice for enantioselective rhodium catalysed conjugate additions. The nature of the proton source is known to be important when enantioselectivity is



Scheme 1 Additional ligand required for enantioselectivity.



Scheme 2 The effect of changing solvent and proton source.

† Electronic supplementary information (ESI) available: experimental procedures and HPLC data. See http://www.rsc.org/suppdata/cc/b4/b406905f/

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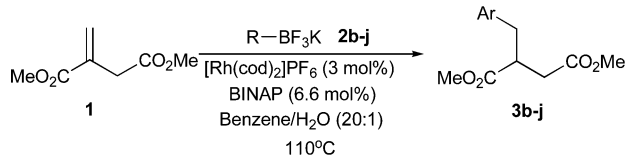
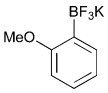
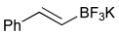
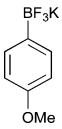
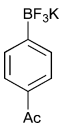
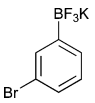
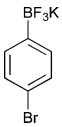
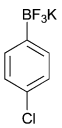
Table 1 Scope of rhodium catalysed conjugate addition–protonation



R-BF_3K		Ligand	Yield (%)[a]	Ee (%)[b]
	**2b**	(*R*)-BINAP	51	68 (*R*)
	**2c**	(*R*)-BINAP	Trace	N.d.
	**2d**	(*R*)-BINAP (*S*)-BINAP	51[c] 82[d]	64 (*R*) 64 (*S*)
	**2e**	(*R*)-BINAP (*S*)-BINAP	89 93	62 (*R*) 56 (*S*)
	**2f**	(*R*)-BINAP (*S*)-BINAP	75 96	48 (*R*) 46 (*S*)
	**2g**	(*R*)-BINAP (*S*)-BINAP	80 93	60 (*R*) 54 (*S*)
	**2h**	(*R*)-BINAP (*S*)-BINAP	85 95	58 (*R*) 62 (*S*)
	**2i**	(*R*)-BINAP (*S*)-BINAP	89 96	60 (*R*) 60 (*S*)
	**2j**	(*S*)-BINAP	80[e]	46 (*S*)

[a] Isolated yield after column chromatography. [b] The absolute configuration of the products were assigned by comparison of the retention time of previously assigned enantiomers using chiral HPLC (Chiracel OD-H, hexane : isopropanol 95 : 5).[5] [c] Isolated with 30% of 3,4-isomer. [d] Isolated with 32% of 3,4-isomer. [e] Isolated with 33% of 3,4-isomer.

dependent on a face selective protonation of the intermediate oxa-π-allylrhodium species.[4c] In this process, the application of sterically-hindered phenols as alternative proton sources revealed a significant correlation between structure and enantioselectivity.[11] However, the system could not be optimized to surpass the reproducible selectivity obtained using water.

The practical utility of the methodology was demonstrated by the addition of a diverse range of trifluoro(organo)borate salts (**2b–j**) (Table 1, ESI†). With the exception of *ortho*-substituted **2c**, the products were isolated in excellent yield and reproducible enantioselectivity. In the presence of (*R*)-BINAP the product with (*R*) configuration was obtained, consistent with *Si* face protonation of the oxa-π-allylrhodium intermediate. Of particular note is the alkenylation process (addition of **2d** and **2j**) which provides products that could not ordinarily be obtained by approaches involving enantioselective hydrogenation.

Finally, it should be pointed out that high temperature (> 100 °C) is essential for enantioselectivity. Attempts to lower the reaction temperature resulted in racemic mixtures of product (**3a–j**).[12] The multifarious factors that control asymmetric induction in the addition to α-substituted activated alkenes are the subject of continued study and will be reported in due course.

The authors would like to thank Johnson-Matthey for the generous loan of transition-metal salts and Professor Richard Jackson (University of Sheffield) for discussion and insightful comments related to the presented work.

Notes and references

1 For reviews see (*a*) T. Hayashi, *Synlett*, 2001, 879; (*b*) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829; (*c*) K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169; (*d*) N. C. O. Tomkinson, *Rodd's Chemistry of Carbon Compounds, Volume V, Topical Volume Asymmetric Catalysis*, Elsevier Science B. V., Amsterdam, 2001, ch. 6.
2 Hayashi has reported that 1-nitrocyclohexene is a satisfactory substrate in the enantioselective addition affording products with high enantioselectivity and good diastereoselectivity controlled by protonation: T. Hayashi, T. Senda and M. Ogasawara, *J. Am. Chem. Soc.*, 2000, **122**, 10716.
3 For a review on the enantioselective protonation of enolates, see: J. Eames and N. Weerasooriya, *Tetrahedron: Asymmetry*, 2001, **12**, 1.
4 (*a*) C. J. Chapman, K. J. Wadsworth and C. G. Frost, *J. Organomet. Chem.*, 2003, **680**, 206; (*b*) M. T. Reetz, D. Moulin and A. Gosberg, *Org. Lett*, 2001, **3**, 4083; (*c*) L. Navarre, S. Darses and J.-P. Genêt, *Angew. Chem., Int. Ed.*, 2004, **43**, 719.
5 For approaches involving asymmetric hydrogenation, see: (*a*) M. J. Burk, F. Bienewald, M. Harris and A. Zanotti-Gerosa, *Angew. Chem., Int. Ed.*, 1998, **37**, 1931; (*b*) W. Tang, D. Liu and X. Zhang, *Org. Lett.*, 2003, **5**, 205.
6 See electronic supporting information for details.
7 For a review see: S. Darses and J.-P. Genêt, *Eur. J. Org. Chem.*, 2003, 4313.
8 Similar results were obtained when the catalyst was pre-treated with hydrogen. A wide range of other ligands were tested and only Tol-BINAP afforded significant enantioselectivity (42%). Selected others; Me-DuPHOS (6%), DIOP (21%), NorPHOS (30%), ^{i}Pr-PHOSOX (10%), ChiraPHOS (< 5%).
9 The two diastereomeric oxa-π-allyl intermediates could interconvert by a π–σ–π mechanism: S. H. Bergens and B. Bosnich, *J. Am. Chem. Soc.*, 1991, **113**, 958.
10 M. Pucheault, S. Darses and J.-P. Genêt, *Eur. J. Org. Chem.*, 2002, 3552.
11 A range of 2,6-disubstituted phenols were also tested resulting in modest enantioselectivities (20–45%).
12 High yields of racemic product **3a** are obtained at 60 °C and 80 °C with either pre-formed complexes or those prepared *in situ*.