

Nickel-catalysed enantioselective hydrovinylation of styrenes in liquid or supercritical carbon dioxide

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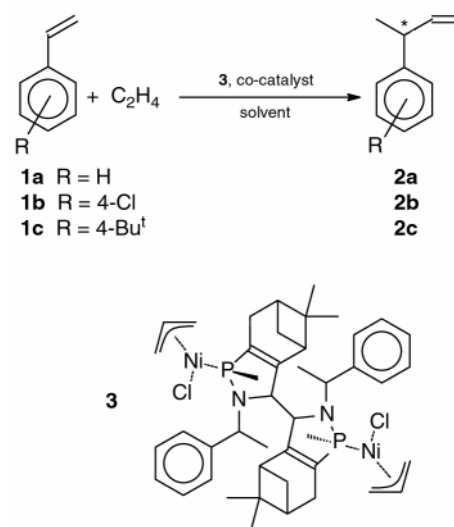
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Compressed (liquid or supercritical) CO₂ is an environmentally benign reaction medium for the highly efficient regio-, chemo- and enantio-selective nickel-catalysed hydrovinylation of styrenes and it allows for catalyst recycling and selective removal of the product from the reaction mixture.

The formation of carbon–carbon bonds is a fundamental operation in synthetic organic chemistry. There is a great demand for catalytic C–C coupling reactions that allow a high level of chemo-, regio- and stereo-selectivity and can be carried out under environmentally friendly conditions. A very efficient catalytic carbon–carbon bond forming reaction is the transition metal catalysed co-dimerisation of alkenes with ethene yielding 3-substituted but-1-enes (hydrovinylation).¹ The hydrovinylation reaction is particularly intriguing because both starting materials are incorporated entirely in the product and the resulting double bond can be used for further transformations to highly functionalised molecules. Wilke *et al.* introduced the (η^3 -allyl)nickel(π) complex **3** (containing a unique chiral 1,2-substituted 1-azaphospholene ligand) as a catalyst precursor for the asymmetric hydrovinylation of aromatic olefins (Scheme 1).^{1,2} Complex **3** catalyses the enantioselective hydrovinylation of styrenes at extremely high rates and with unrivalled chemo-, regio- and enantio-selectivity, but it needs to be activated by an excess of highly flammable Et₃Al₂Cl₃. Furthermore, the reaction requires temperatures below –60 °C and the use of toxicologically disreputable CH₂Cl₂ as a solvent.

In order to overcome these drawbacks, we investigated the hydrovinylation with complex **3** in liquid and supercritical CO₂ as an alternative solvent.^{3,4} The reaction proceeded smoothly using Et₃Al₂Cl₃ as the co-catalyst, but ees were disappointingly low (Table 1). We also observed some corrosion of the stainless steel high pressure reactor under these conditions, and therefore tried to replace the aggressive Lewis acid by weakly co-ordinating anions which are easier to handle and non-corrosive under the reaction conditions. Unfortunately, no catalytic

activity was observed using TfO[–] or [Al(O(CH₂)₂C₆F₁₃)₄][–] as co-catalysts. The use of [Al(OC(Ph)(CF₃)₂)₄][–] led to an active catalytic system but reactivity and stereoselectivity were low. Finally, we were pleased to find that the use of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) yields a catalytic system that is comparable to Et₃Al₂Cl₃ in activity and chemoselectivity but gives far better ees.[†] The use of BARF activates **3**, increases the thermal stability of the catalyst, and provides sufficient solubility of the active species in liquid and supercritical CO₂,⁵ thus allowing the reaction to proceed close to and beyond the critical point of pure CO₂ (*T*_c = 31 °C, *P*_c = 73 atm, *d*_c = 0.468 g cm^{–3}). The 4-substituted styrenes **1b,c** were also successfully reacted with ethene in liquid and supercritical CO₂ to yield **2b,c** in high yield and with high ee. We note that **2c** is a key intermediate in a potential route to the non-steroidal anti-inflammatory drug IbuprofenTM.¹



Scheme 1

Table 1 Enantioselective hydrovinylation of styrenes **1a–c** in CO₂^a

Substrate/ product	Co-catalyst	<i>T</i> /°C	Conversion ^b (%)	Selectivity ^{b,c} (%)	Ee of 2 ^b (%)
1a/2a	Cl ₃ Al ₂ Et ₃	1	> 99	92.9	70.2 (<i>R</i>)
1a/2a	TfO [–]	40	< 1.0	—	—
1a/2a	[Al(O(CH ₂) ₂ C ₆ F ₁₃) ₄] [–]	22	0	—	—
1a/2a	[Al(OC(Ph)(CF ₃) ₂) ₄] [–]	22	35	94.3	76.0 (<i>R</i>)
1a/2a	BARF	1	> 99	88.9	86.2 (<i>R</i>)
1a/2a	BARF	23	> 99	71.4	85.6 (<i>R</i>)
1a/2a	BARF	40	> 99	74.9	83.6 (<i>R</i>)
1a/2a	BARF	35 ^d	> 99	38.9	91.6 (<i>R</i>)
1b/2b	BARF	40	> 99	80.5	81.0 (—)
1b/2b	BARF	24	> 99	87.0	81.3 (—)
1c/2c	BARF	35 ^e	> 99	44.4	89.4 (<i>R</i>)
1c/2c	BARF	20 ^e	75.8	71.4	76.6 (<i>R</i>)

^a For standard reaction conditions see note [†]. ^b Determined by GC analysis. ^c Fraction of **2** in product mixture. Typical by-products were 2-phenylbut-2-enes and hydrovinylation products of **2**. ^d Reaction time 30 min. ^e Reaction time 50 min.

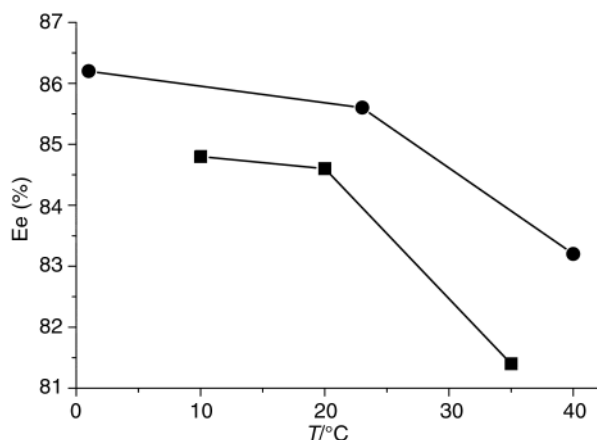


Fig. 1 Enantiomeric excess of **2a** obtained from hydrovinylation using the 3-NaBARF catalyst in (●) CO₂ and (■) CH₂Cl₂ at different temperatures.

In hydrovinylation, the positive 'BARF effect' on the thermal stability of catalyst is not limited to scCO₂ as a solvent.⁶ This anion can also be used as co-catalyst with **3** for the hydrovinylation of **1a** in CH₂Cl₂ and, at temperatures above 0 °C, proves to be superior to Et₃Al₂Cl₃ in terms of enantioselectivity (84.8 vs. 70.2% at 1 °C) with similar chemo- and regioselectivities. However, a comparison of the solvents CO₂ and CH₂Cl₂ reveals that enantioselectivity is generally better in CO₂ (Fig. 1). Chemoselectivity for **2a** is also considerably higher in CO₂ at elevated temperatures; 57.2% selectivity for **2a** are observed in CH₂Cl₂ at 35 °C compared to 74.9% in scCO₂ at 40 °C, with complete conversion in both cases.

In scCO₂, the catalyst formed from **3** and NaBARF exhibits remarkable stability as demonstrated in an experiment at 40 °C where a **1a**:Ni ratio of 10 000:1 was used (Fig. 2). With an initial turnover frequency of greater than 1300 h⁻¹, a total turnover number of 5000 (corresponding to 50% conversion) was achieved. This result is quite remarkable because previously reported turnover numbers for other nickel-catalysed reactions in the presence of scCO₂ were below 22.⁷ A catalyst formed from [Ni(cod)₂] and PEt₃ was found to be highly susceptible to ligand oxidation in scCO₂, resulting in the formation of nickel carbonyls and the corresponding phosphin-oxides.^{7c} In the experiment shown in Fig. 2, the desired product **2a** was formed with extremely high chemoselectivity and no other products could be detected by NMR or GC analyses. The ee of 79.8% was only slightly lower than in experiments leading to complete conversion of **1a**.

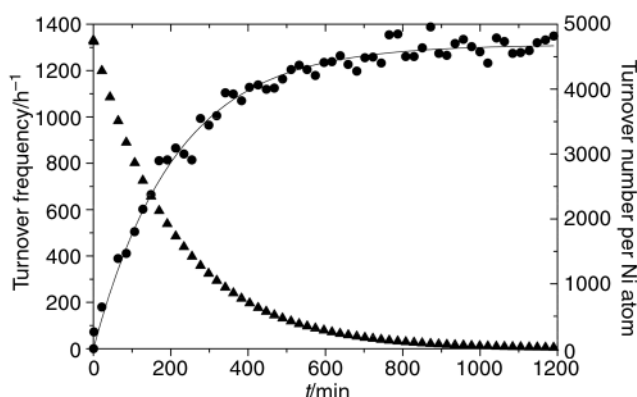


Fig. 2 (●) Turnover number of hydrovinylation of **1a** in the presence of 3-NaBARF (**1a**:Ni = 10.000) in CO₂ at 40 °C. (▲) Turnover frequencies, derived from the first derivative of the least-squares fit of the turnover number data.

Another intriguing feature of our new procedure for hydrovinylation is the difference in product distribution of the condensate collected from the cold trap and the residue in the high pressure vessel. If the reactor was vented at temperatures above *T_c* of pure CO₂, the trap content was considerably enriched with **2a** (e.g. 81.0 vs. 60.5% in the residue) and contained less of the by-products formed from isomerisation and hydrovinylation of **2a**. This finding indicates that it is possible to remove **2a** selectively from the reaction mixture with CO₂. Additionally, the catalyst can be easily recycled after venting and removal of all volatiles *in vacuo*. At a reaction temperature of 22 °C, the ee was minimally reduced (from 83.4% at the beginning down to 79.8%), but some loss in activity was observed (from >99% conversion down to 33% conversion of **1a**) in four subsequent runs.

In summary, we obtained highly promising results performing enantioselective nickel-catalysed hydrovinylation in liquid and supercritical CO₂. The attractive prospects for catalyst recycling and selective removal of the product encourage our ongoing efforts to explore CO₂ as a solvent for enantioselective catalysis.

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Notes and references

† In a typical experiment, a stainless steel high pressure reactor (*V* = 27 cm³) equipped with thick-wall glass windows, a PTFE stirring bar, a bore hole for a thermocouple, and needle and ball valves was charged with NaBARF (33.4 mg, 35.5 × 10⁻³ mmol) under argon. A dosing unit containing a solution of **3** (5.4 mg, 6.3 × 10⁻³ mmol) in **1a** (450 mg, 4.37 mmol) was connected to the reactor through the closed ball valve and pressurised with CO₂ (7.1 g). The reactor was filled through the needle valve with ethene (1.1 g, 39.3 mmol) and CO₂ (14.6 g) using a compressor. The reaction mixture was then warmed to 40 °C, while the dosing unit was heated to 60 °C. Opening the ball valve started the reaction, which was allowed to proceed for 15 min. The reactor contents were then vented through a trap cooled to -55 °C. The products were collected separately from the trap and the reactor by extraction with Et₂O or acetone and analysed by GC and NMR.

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