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Tsuji–Trost allylation of CH acids in supercritical carbon dioxide: advantages and problems

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The Pd(PPh₃)₄-catalyzed reaction between α -cyano or β -oxo carboxylates and allyl acetate in supercritical carbon dioxide with the K₂CO₃-18-crown-6 system as a base affords exhaustive allylation products in high yields, whereas malononitrile and acetylacetone of higher CH acidity form the mixtures of mono- and diallylated derivatives in moderate yields.

Previously,¹ we have pioneered in the Tsuji–Trost allylation² in supercritical carbon dioxide (scCO₂) using the asymmetric coupling of dimethyl malonate and prochiral 3-acetoxy-1,3-diphenylpropene as an example. The greatest challenge in such a processing was to provide effective CH-acid deprotonation because traditional deprotonating agents such as NaH and LDA (for full preliminary CH-acid deprotonation) or the BSA-AcONa system (for gradual deprotonation in the course of reaction) in organic solvents seem incompatible with the electrophilic character of carbon dioxide. Luckily, we used cesium carbonate for the gradual deprotonation of dimethyl malonate in scCO₂ thus allowing the coupling to proceed well at 40-75 °C and 110-240 atm (an optimum pressure was 170 atm); the application of chiral ligands resulted in products with ee up to 90%.¹ However, a change from active 3-acetoxy-1,3-diphenylpropene to other allylating agents led to a low conversion; this was likely due to the insufficient steady-state concentrations of both reaction species.

Here, we used the CH acids that are stronger than dialkyl malonate **1a** ($pK_a \sim 16.4$)³ and whose deprotonation with a heterogeneous base in almost nonpolar scCO₂ occurs more readily, which should increase the steady-state concentration of a carbanion. Scheme 1 and Table 1 summarize the results obtained[†] using allyl acetate (AllOAc) and trivial Pd(PPh₃)₄ as a catalyst. Based on our previous findings,¹ the reaction pressure was 170 atm in all cases. At 75 °C, malonate **1a** was predominantly monoallylated with Cs₂CO₃ used as a base, whereas no reaction occurred with a less soluble system of K₂CO₃ and a 18-crown-6 additive (Table 1, entries 1, 2). The formation of product **2a** can be rationalized based on essentially greater values of pK_a (>18)³ for C-substituted malonates.

As expected, ethyl acetoacetate **1b** (p $K_a \sim 14.4$) and ethyl cyanoacetate **1c** (p $K_a \sim 13.1$) of higher CH acidity were readily



Scheme 1 Reagents and conditions: i, AllOAc, [Pd], base, $scCO_2$ (170 atm), Δ , 18 h (Table 1); ii, AllOAc, Pd(PPh₃)₄, K₂CO₃, 18-crown-6, CH₂Cl₂, room temperature, 18 h.

transformed into their diallylated derivatives **3b**,**c** in good yields (Table 1, entries 3, 4, 7–9).[‡] Not only Cs_2CO_3 but also much less expensive K_2CO_3 can be used as a base for this purpose. Note that, in the case of cyanoacetate **1c**, the 18-crown-6 additive was not so crucial (Table 1, entries 8, 9) as in the case of acetoacetate **1b** (entry 4). Lowering the temperature to 50 °C resulted in

Table 1 Allylation of CH acids 1a-e in supercritical CO2.4

Entry	Substrate $(pK_a)^3$	Base	T/°C	GC data (%)		
				1	2	3
1	1a (16.4)	Cs ₂ CO ₃	75	12	84	4
2	1a	K ₂ CO ₃ /18-crown-6	75	100	_	_
3	1b (14.4)	Cs ₂ CO ₃	75	_	_	100
4	1b	K ₂ CO ₃ /18-crown-6 ^b	75	_	_	100 (87) ^c
5	1b	K ₂ CO ₃ /18-crown-6	50	_	80	20
6	1b	K ₂ CO ₃ /18-crown-6	75^d	_	52	48
7	1c (13.1)	Cs ₂ CO ₃	75	_	_	100
8	1c	K ₂ CO ₃ /18-crown-6 ^e	75	_	_	100 (91) ^c
9	1c	K ₂ CO ₃	75	_	_	100
10	1c	K ₂ CO ₃ /18-crown-6	50	44	35	21
11	1c	K ₂ CO ₃ /18-crown-6	75^d	3	44	53
12	1d (13.3)	K ₂ CO ₃ /18-crown-6	75	_	$(18)^{c}$	$(23)^{c}$
13	1e (11.0)	K ₂ CO ₃ /18-crown-6	75	_	(6) ^c	$(22)^{c}$
14	1e	K ₂ CO ₃ /18-crown-6	75^e	_	_	(36) ^c

^{*a*} 1 mmol of CH acid **1**, 3 mmol of AllOAc, 2.5 mmol of a base, 2 mol% Pd(PPh₃)₄, 5 mol% 18-crown-6 (if taken), 10 ml autoclave, 170 atm scCO₂, 18 h heating. ^{*b*} No reaction without 18-crown-6. ^{*c*} Isolated preparative yields are given in parentheses. ^{*d*} Catalyst, Pd₂dba₃/2 dppe. ^{*e*} The same loading in a 2 ml autoclave.

[‡] In cases of ethyl acetoacetate **1b** and acetylacetone **1d**, O-allylation products were not detected.

[†] Allylation of CH acids in scCO₂. Catalyst Pd(PPh₃)₄ (23 mg, 0.02 mmol), CH acid **1a–e**, **4** or **5** (1 mmol), allyl acetate (0.3 ml, ~3 mmol), K₂CO₃ (345 mg, 2.5 mmol) and 18-crown-6 (13 mg) were placed in a 10 ml autoclave open to air (in some experiments, other bases or catalysts were used in equivalent amounts; when the CH acids were **4** and **5**, the base amount was halved). The vessel was filled with scCO₂ to a total pressure of 60 atm. The mixture was equilibrated at a reaction temperature (30 min); then, additional CO₂ was pumped to adjust a pressure of 75 atm. After this, the mixture was stirred for 18 h at a specified temperature. The vessel was cooled and slowly depressurized. The autoclave contents were treated with CH₂Cl₂, filtered through silica gel and concentrated. The residue was analyzed by GC and/or subjected to column chromatography (silica gel, gradient 0 \rightarrow 6% EtOAc in light petroleum) to afford products **2**, **3**, **6**, **7**, **9** whose NMR-spectroscopic data were close to those reported earlier (see Online Supplementary Materials).

incomplete conversion, and monoallylation products **2b**,**c** were detected (entries 5, 10). The catalyst prepared from Pd_2dba_3 and 1,2-bis(diphenylphosphino)ethane (dppe) in CH_2Cl_2 was less effective than $Pd(PPh_3)_4$ (entries 6, 11).

Similar reactions of acetylacetone 1d[§] and malononitrile 1e afforded the mixtures of mono- (2d,e) and diallylation (3d,e) products in moderate total yields (Table 1, entries 12, 13). In these cases, GC analysis could not be used to monitor the composition of the mixtures because substrates 1d,e and monoallylated compounds 2d,e were undetectable (moreover, they can occur as potassium derivatives due to their high acidity). Therefore, the preparative yields of isolated materials were used to characterize the efficiency of these processes. The moderate yields of products 2d,e and 3d,e can be attributed to the lower nucleophilicity of 1d,eand 2d,e-derived carbanions. This result allowed us to conclude that the dependence of the yield of an allylation product on the CH acidity of a XCH₂Y substrate approaches a maximum value at p K_a 13–14: less acidic substrates are difficult to deprotonate while more acidic ones form low-nucleophilicity carbanions. When malononitrile 1e was allylated in an autoclave of five times smaller volume with the same loading of reactants (to diminish dilution), the yield of product 3e was somewhat higher (entry 14), however, it remained far from quantitative.

Substrates 4 $(pK_a \sim 7.5)^4$ and 5 $(pK_a \sim 10.15)^5$, which are more acidic than 1d,e but have only one active proton, afforded allylation derivatives 6, 7 in good yields (Scheme 2).

The prenylation of cyanoacetate **1c** with 3-acetoxy-3-methylbut-1-ene **8** (Scheme 3) in scCO₂ gave in a total yield of 25% a mixture of two expected normal (**9**) and iso (**9**') products and isopentenyl analogues **9**'' and **9**''' bearing C₅H₉ substituents of the same skeleton with other positions of double bonds and linkage sites (as judging from ¹H NMR-spectroscopic and GC-MS data) in a ratio of ~18:32:21:29. Similar isomerization within prenyltype π -allylic metal complexes leading to such by-products was indicated earlier;⁶ it seems possible to occur at the elevated temperature of our experiment. Previously,^{7(a)} we have reported that the K₂CO₃-promoted prenylation of cyanoacetate **1c** in DMF at 20 °C quantitatively afforded only isomers **9** and **9**' in ratios depending on the ligand applied.

Note that substrates **1a–e** and **4** in dichloromethane at 20 °C give exhaustive allylation products in very good yields (for the conditions, see ref. 7 and Online Supplementary Materials).



Scheme 2 Reagents and conditions: i, AllOAc, Pd(PPh₃)₄, K₂CO₃, 18-crown-6, scCO₂ (170 atm), 75 °C, 18 h.

§ Judging from ¹H NMR spectra, monoallylacetylacetone 2d in CDCl₃ exists as a mixture of enol and keto forms in a 1:1 ratio.



In the conclusion, the Tsuji–Trost reaction can be performed in $scCO_2$, although it turned to be very substrate-dependent under studied conditions. However, the use of $scCO_2$ in such a crosscoupling can be promising in industry because the advantages of $scCO_2$ as a reaction medium are well-recognized.⁸

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.03.009.

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