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# An enantioselective indium-mediated allylation reaction of aldehydes and ketones in dichloromethane

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### Abstract

An enantioselective indium-mediated addition reaction of allylic bromides to carbonyl compounds was achieved in dichloromethane in the presence of (-)-cinchonidine. The desired products were obtained in moderate to excellent yields and with up to 75% enantioselectivity. © 1999 Elsevier Science Ltd. All rights reserved.

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To date, several enantioselective metal-mediated addition reactions of allylic halides to carbonyl compounds have been reported. Most of these reactions were carried out in solvating ethereal solvents.<sup>1-3</sup> However, to the best of our knowledge, the non-coordinating solvent dichloromethane was never employed. Herein, we present one of the first examples under this category. In our system the metal is indium<sup>4</sup> and the chiral ligand is (–)-cinchonidine (Scheme 1).



1 (-)-cinchonidine

Scheme 1.

Our protocol was as follows. A mixture of dry (–)-cinchonidine (2 equivalents), indium powder (2 equivalents) and an allylic bromide (6 equivalents) in a dry solvent (6 mL/1 mmol of the carbonyl compound) were stirred at room temperature to give a clear solution<sup>5</sup> (usually it took 30 to 60 minutes, depending on the bromide). A certain amount of dry hexane and an additive were added, followed

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entry	R'COR''	Bromide	Solvent	Temp.	Additive	yield	eeª
			-	(°C)		(%)	(%)
1	PhCOCF <sub>3</sub>	allyl	THF/Hex 3:1	-78	-	74	57
2	PhCOCF <sub>3</sub>	allyl	THF/Hex 3:1	25	-	100	62
3	$PhCOCF_3$	allyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1	-78	-	63	64
4	$PhCOCF_{3} \\$	allyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1	25	-	63	<b>70</b> 7
5	PhCOCF <sub>3</sub>	allyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1	25	Lutidine(0.2 eq)	83	66
6	$PhCOCF_3$	allyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1	25	EtN <sup>i</sup> Pr <sub>2</sub> (0.2 eq)	83	72
7	$PhCOCF_3$	allyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1	25	$EtN^{i}Pr_{2}(1.0 eq)$	80	70
8	$PhCOCF_3$	allyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:0.9	25	-	<b>6</b> 1	60
9	PhCHO	allyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1	25	-	55	<b>75</b> <sup>8</sup>
10	PhCHO	allyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1.5	25	-	54	74
11	PhCHO	prenyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1	25	-	100	59
12	PhCHO	prenyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:1.7	25	-	98	73
13	PhCHO	prenyl	CH <sub>2</sub> Cl <sub>2</sub> /Hex 3:3	25	-	100	<b>74</b> <sup>8</sup>

 Table 1

 Reaction conditions for the enantioselective allylation

<sup>a</sup> Determined by HPLC analysis employing a Daicel Chiracel OD column. Absolute configuration assignment by comparison with literature value of optical rotation.

by the introduction of the carbonyl compound (1 equivalent). The reaction was stirred for 5 hours before being quenched with dilute hydrochloric acid and routine workup. The effects of the reaction temperature, solvents and additives were studied in detail. The results are presented in Table 1. Firstly, THF and dichloromethane were compared as the major component of a 3:1 mixed solvent system with hexane,<sup>6</sup> using 2,2,2-trifluoroacetophenone and allyl bromide as the reactants. Though in general the isolated yields of the desired homoallylic alcohol were higher in THF, the enantioselectivities showed an opposite trend (entries 1-4). Secondly, when the temperature effect was investigated, to our surprise, in both solvent systems the stereoselectivities increased as the reaction temperature was increased from -78°C to 25°C. Thirdly, the allyl transfer process was accelerated in the presence of either lutidine or diisopropylethylamine, however, no dramatic improvement of stereoselectivities was observed. The 2,6-dialkylated pyridine was detrimental to the selectivity while the tertiary amine only led to a slight increase in this aspect. Fourthly, the solvent influence was surveyed in detail with benzaldehyde. With allyl bromide (entries 8–10), the highest enantioselectivity was reached when a mixture of 3:1 CH<sub>2</sub>Cl<sub>2</sub> and hexane was utilized. Further increase in hexane percentage did not improve the result. With prenyl bromide (entries 10-13), a similar trend was observed, except that a higher ratio of hexane was used (CH<sub>2</sub>Cl<sub>2</sub>:hexane 3:1.7). Fifthly, the chiral ligand (-)-cinchonidine could be almost quantitatively recovered after reaction by acid-base workup.

The optimized reaction conditions were applied to other carbonyl substrates and the results are summarized in Scheme 2. There are several points to note. Firstly, in all cases moderate to excellent yields were obtained. Secondly, for the reactions of both 2-pyridine and 2-quinoline carboxaldehydes, the selectivities were poor, probably due to competitive binding of the nitrogen atoms to the indium center. Thirdly, the allylation reactions of methyl ketones usually did not provide satisfactory stereocontrol. Fourthly, in the case of benzyl acetoacetate, no detectable homoallylic alcohol was observed with all the  $\beta$ -ketoester being recovered. This is probably because of the acidity of the  $\alpha$ -protons.



#### Scheme 2.

In summary, an enantioselective coupling of allylic bromides and carbonyl compounds in dichloromethane was achieved in the presence of indium and (–)-cinchonidine. In some cases, good enantioselectivities were obtained and, in particular, a 70% ee was obtained in the allylation of 2,2,2trifluoroacetophenone. The compatibility of dichloromethane with the allylic indium species is in contrast to the common practice that the chlorinated solvent is not a choice for the Grignard-type organometallic reagents.<sup>9</sup> Further work such as ligand re-designing is still underway in our laboratory.

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- 5. We noticed that in the absence of (-)-cinchonidine, indium could not insert into the allylic bromides at room temperature in dichloromethane. In other words, the ligand facilitated the formation of allylic indium species, although the mechanism is unclear.
- 6. Other solvents (such as toluene and diethyl ether) were also tried, however the allylindium complex with (-)-cinchonidine could not form.

- 7. Due to lack of its immediate derivatives with fully assigned stereochemistry, the absolute configuration of  $\alpha$ -(2-propenyl)- $\alpha$ -trifluoromethylbenzenemethanol ( $[\alpha]_D^{25}$ =-45.97 (c 0.34, benzene)) was tentatively assigned to be (S). In the PhCOR series, the steric bulkness of R increases in the order of PhCHO (R=H), PhCOMe (R=Me) and PhCOCF<sub>3</sub>(R=CF<sub>3</sub>), while the enantiomeric enrichment went through a valley in the same series (75% ee for R=H; 2% ee for R=Me: 70% ee for R=CF<sub>3</sub>). Assuming similar binding modes of the carbonyl substrates to the allylindium species, we suggest the absolute configuration of the allylated product of RCOCF<sub>3</sub> is opposite to that of PhCHO.
- 8. The absolute stereochemistry of  $\alpha$ -(2-propenyl)benzenemethanol was determined to be (*R*) based on its optical rotation ( $[\alpha]_D^{25}$ =+48.67 (*c* 0.42, benzene)). And the absolute stereochemistry of  $\alpha$ -(1,1-dimethyl-2-propenyl)benzenemethanol was assigned to be (*R*) by analogy ( $[\alpha]_D^{25}$ =+29.92 (*c* 0.64, benzene)). Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, 60, 3697–3704.
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