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BINOL-Ti-Catalyzed Synthesis of Tertiary Homoallylic Alcohols: The First Catalytic Asymmetric Allylation of Ketones

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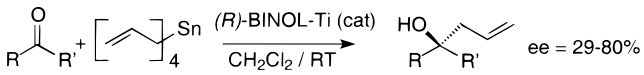
ABSTRACT



The first catalytic asymmetric allylation of simple ketones is realized using tetraallyltin as allylating reactant and BINOL-Ti as chiral catalyst. Fast reaction, good yield, and moderate enantioselectivity is achieved with aromatic and α,β-unsaturated ketones, while aliphatic ketones afford lower enatiomeric excess.

The enantioselective synthesis of homoallylic alcohols has acquired a major role among the organic synthetic methodologies thanks to the versatility and good chemical stability of the target product. The development of asymmetric catalytic processes for obtaining *secondary* homoallylic alcohols from aldehydes and allyltrialkylstannanes[1] or allyltrialkylsilanes[2] greatly enhances the potentiality of this synthetic tool. However, the cited processes fail to give any product when applied to ketones. Actually, very few catalytic enantioselective additions of carbon nucleophiles to unactivated ketones have been achieved successfully[3] and, to the best of our knowledge, such processes do not include allylation.

The highly enantioselective allylation of aliphatic ketones has been realized quite recently by Tietze et al.[4] through the use of a pseudoephedrine derivative as a stoichiometrical chiral auxiliary. Using a different approach, Baba et al.[5] have found that tetraallyltin adds to acetophenone in 60% ee in the presence of 2 mol equiv of 1,1′-binaphthalene-2,2′-diol (BINOL). The authors attribute to BINOL the role of a chiral activator: tetraallyltin is transformed into an enantiopure, more reactive, aryloxyallyltin reagent by a protolytic ligand exchange between BINOL and one or more allyl groups.

Starting from our precedent experience in the asymmetric allylation of aldehydes with BINOL titanium[1a] and zirconium[1c,g] catalysts, and exploiting the good reactivity of tetraallyltin, we have faced the challenging problem of the catalytic asymmetric allylation of ketones. We present here some preliminary results obtained from the use of the BINOL/$TiCl_2$(O*i*-Pr)$_2$ catalyst.

The catalyst was prepared in situ by two different procedures (Scheme 1): equimolar amounts of BINOL and $TiCl_2$(O*i*-Pr)$_2$ were treated with 2 mol equiv of allyltributyltin (**3a**)[6] or tetraallyltin (**3b**) to afford **Cat(A)** and **Cat(B)**, respectively, which were used in various catalytic ratios to

(1) (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (c) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897. (e) Weigand, S.; Brückner, R. *Chem. Eur. J.* **1996**, *2*, 1077. (f) Yanagisawa, A.; Nakashima, H.; Ishiba, A., Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723. (g) Casolari, S.; Cozzi, P. G.; Orioli, P.; Tagliavini, E.; Umani-Ronchi, A. *Chem. Commun.* **1997**, 2123. (h) Yu, C.-M.; Choi, H.-S.; Jung, W.-H.; Kim, H.-J.; Shin, J. *Chem. Commun.* **1997**, 761. (i) Yu, C.-M.; Yoon, S.-K.; Choi, H.-S.; Baek, K. *Chem. Commun.* **1997**, 763. A more complete reference list can be found in: Cozzi, P. G.; Tagliavini, E.; Umani-Ronchi, A. *Gazz. Chim. Ital.*, **1997**, *127*, 247.

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(4) (a) Tietze, L. F.; Schiemann, K.; Wegner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851. (b) Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1998**, *4*, 1862.

(5) Yasuda, M.; Kitahara, N.; Fujibayashi, T.; Baba, A. *Chem. Lett.* **1998**, 743.

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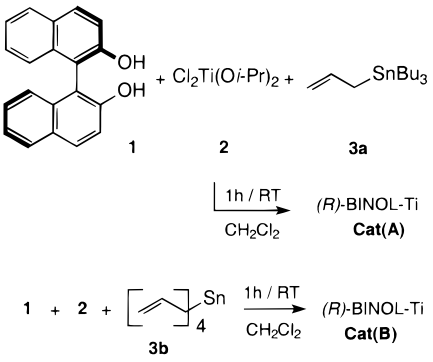
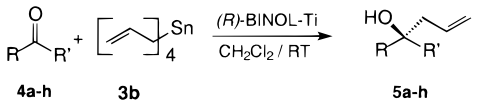
Scheme 1



promote the addition of tetrallyltin to ketones (**4a**−**h**) in CH_2Cl_2 at room temperature, giving tertiary homoallylic alcohols (**5a**−**h**) as shown in Scheme 2.

Scheme 2



a: R= Ph; R'= Me
b: R= 2-Naphtyl; R'= Me
c: R= 4-(MeO)-C_6H_4; R'= Me
d: R= 4-(Me)-C_6H_4; R'= Me
e: R= 4-(NO_2)-C_6H_4; R'= Me
f: Tetralone
g: R= *(E)*-PhCH=CH; R'= Me
h: R= *n*-C_6H_{13}; R'= Me

A few reaction conditions were screened using acetophenone **4a** and 2-naphthyl methyl ketone **4b** as model substrates. These results are collected in Table 1.

The allylation reaction proceeds smoothly on both substrates with 20% mol of catalyst in CH_2Cl_2 at room temperature, in good to excellent chemical yields, and moderate enantioselectivity (ee = 64% for **4a** and 51% for **4b**). Lowering of the temperature reduces the reactivity but does not affect the stereoselectivity (run 3); while upon changing the solvent to toluene or ether (runs 6 and 7), the enantiocontrol is lost. Both substrates are quite sensitive to the catalytic ratio: a top enatiomeric excess level of 65% and 80%, respectively, for **4a** and **4b** is reached at different values (20% and 40%) of catalyst loading (runs 1, 2, and 4, and 9, 10, and 11).

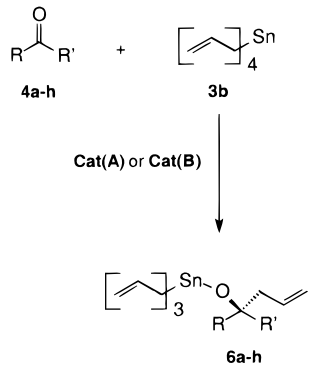
Table 1. Enantioselective Allylations of Acetophenone (**4a**) and 2-Naphthyl Methyl Ketone (**4b**)[a]

run	ketone	cat. (mol %)	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1	**4a**	A (10)	CH_2Cl_2	1.5	78	55
2	**4a**	A (20)	CH_2Cl_2	2	77	65
3	**4a**[d]	A (20)	CH_2Cl_2	19	76	64
4	**4a**	A (30)	CH_2Cl_2	1	95	64
5	**4a**	B (20)	CH_2Cl_2	20	75	52
6	**4a**	A (20)	toluene	96	69	6
7	**4a**	A (10)	Et_2O	20	53	6
8	**4b**	A (20)	CH_2Cl_2	1.5	87	51
9	**4b**	B (20)	CH_2Cl_2	17	70	37
10	**4b**	B (40)	CH_2Cl_2	4	94	80
11	**4b**	B (100)	CH_2Cl_2	3	88	81

[a] All the reactions were carried out at room temperature with a **4**:**3b** = 1:1.5 molar ratio unless otherwise stated. [b] Yield of purified products. [c] Determined by HPLC on CHIRACEL OD column. [d] Reaction performed at 0 °C.

The reasons why the enantioselectivity of an asymmetric catalytic reaction is significantly affected by the catalyst ratio is often difficult to ascertain, the most probable one being a competitive, nonstereoselective reaction pathway. We can exclude a contribution from the direct reaction between **3b** and the ketone, since we have verified that a mixture of **3b** and **4a** in CH_2Cl_2 does not afford any homoallylic alcohol product after 48 h at room temperature. Another possible pathway to the racemic product is based on the increased reactivity of the allylating agent during the course of the reaction. The kinetic trend of the allylation of aldehydes with **3b** has been studied by Young et al.[7] Indeed, they found that the reaction shows an induction period, followed by a strong acceleration and fast, complete conversion of reagents into products. This trend was attributed to the successive formation of mono-, di-, and trialkoxyallyltin species, whose reactivity toward aldehydes increases each time. In our case, a reasonable mechanism implies that the product of each catalytic cycle is an alkoxytriallylstannane **6**, more nucleophilic than the parent **3b** (Scheme 3). This new species (or polyalkoxyallylstannanes) could be responsible for the uncatalyzed formation of a significant amount of product; in this case a higher enatiomeric excess of the product should be observed in the first stage of the reaction. However, monitoring of run 2 of Table 1 at 31% and 95% conversion gave enatiomeric excess values identical to those found after completion, ruling out this possibility.

Scheme 3



(6) Allyltributyltin is protolyzed by a mixture of BINOL and $TiCl_2(Oi\text{-}Pr)_2$ affording propene, tributyltin chloride, and the active BINOL-Ti catalyst. The real nature of such catalyst is under investigation by our group.

(7) Cokley, T. M.; Harvey, P. J.; Marshall. R. L.; McCluskey, A.; Young, D. J. *J. Org. Chem.* **1997**, *62*, 1961.

The absolute configuration of the product **5a** was determined by comparison of the sign of the optical rotation with the literature value.[8] The *re* face of the ketone is attacked when the *(R)*-catalyst is used, in agreement with the constant preference shown by BINOL-based catalysts.[1]

Later we extended our screening to different aromatic and aliphatic ketones using 20% mol of **Cat(A)**, room temperature, and CH_2Cl_2 as solvent. The results are collected in Table 2.[9]

Table 2. Allylation of Various Ketones[a]

ketone	*t* (h)	yield (%)[b]	ee (%)[c]
4a	2	77	65
4b	1.5	87	51
4c	24	75	44
4d	21	85	55
4e	3	80	47
4f	20	91	35
4g	1	83	51
4h	3	89	29[d]

[a] All the reactions were carried out at room temperature with a **4**:**3b**:**Cat(A)** = 1:1.5:0.2 molar ratio. [b] Yield of purified products. [c] Determined by HPLC on CHIRACEL OD column. [d] Determined by GC on MEGADEX 5 column.

Moderate enantioselectivities are obtained from substituted acetophenones, with only marginal influence from the electronic properties of the substituent. Also the rigidity of the cyclic structure of tetralone is not beneficial, since the product **5f** is obtained in only 35% ee. The enone **4g** undergoes exclusively 1,2-addition in fair enatiomeric excess. The regioselectivity of the addition to carbonyl was already observed by Baba[5] in the BINOL-promoted reaction on the same substrate, but in that case a lower enatiomeric excess was achieved.

Finally, simple dialkyl ketones, like 2-octanone, afforded the nonracemic tertiary alcohol **5h**, although the enatiomeric excess is modest. However, discrimination between methyl and *n*-alkyl substituents is noticeable and is promising for the development of our research.

The results presented in this paper are partially satisfactory in terms of enantiocontrol. We consider therefore our study only a preliminary investigation. Nevertheless, we have demonstrated the possibility of realizing a catalytic enantioselective synthesis of tertiary homoallylic alcohols by means of an easily available, well-established chiral catalyst, a goal that was far from obvious. We believe that further effort in this direction will afford a powerful synthetic methodology for the synthesis of quarternary stereogenic carbon centers in a highly enantioselective fashion.

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Supporting Information Available: Full experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Ishizaki, M.; Soai, K.; Yokoyama, S. *Chem. Lett.* **1987**, 341.

(9) **Typical procedure**: A mixture of *(R)*-(+)-1,1′-binaphthol (**1**) (28.6 mg, 0.1 mmol), $TiCl_2(Oi\text{-}Pr)_2$ (**2**) 0.5 M in toluene (0.2 mL, 0.1 mmol), and allyltributyltin (**3a**) (0.062 mL, 0.2 mmol) in 2 mL of dichloromethane was stirred at room temperature under anhydrous atmosphere for 1 h. To the solution of **Cat(A)** thus prepared, acetophenone (**4a**) (0.058 mL, 0.5 mmol) and tetraallyltin (**3b**) (0.180 mL, 0.75 mmol) were consecutively added. After 2 h, the reaction was quenched by the addition of HCl 0.1 M (0.5 mL) and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, concentrated, and purified by flash cromatography to afford **5a** in 77% yield and 65% ee. For the reactions promoted by **Cat(B)**, the same procedure was applied using tetraallyltin (**3b**) (0.048 mL, 0.2 mmol) instead of allyltributyltin.