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Catalytic Asymmetric Carbonyl-Ene Reactions with Alkynylogous and Vinylogous Glyoxylates: Application to Controlled Synthesis of Chiral Isocarbacyclin Analogues

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Abstract: *The asymmetric carbonyl-ene reaction with alkynylogous and vinylogous glyoxylates (**1**, **2**) catalyzed by a binaphthol-derived chiral titanium complex is described. The catalytic asymmetric ene reaction with aldehyde (**1**) can be applied to the double asymmetric synthesis of isocarbacyclin analogues bearing a 2-allenyl side chain.* Copyright © 1996 Elsevier Science Ltd

Recently, the catalytic asymmetric carbonyl-ene reaction with glyoxylates as highly reactive enophiles using a chiral Lewis acid, has emerged as an efficient method for asymmetric synthesis.[1] We report herein new type carbonyl enophiles that include alkynylogous glyoxylate (3-formylpropiolate, **1**[2]) and vinylogous glyoxylate ((*E*)-3-formylacrylate, **2**[3]) (Fig. 1). These carbonyl enophiles can be used in asymmetric carbonyl-ene reactions that are catalyzed by the binaphthol-derived chiral titanium complex.[4] Furthermore, the efficient use of these carbonyl enophiles in the key step of asymmetric synthesis of isocarbacyclin analogues is described.[5]

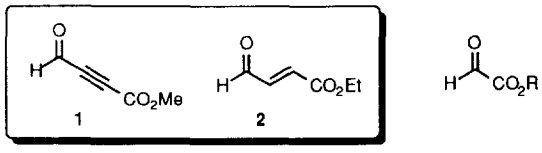


Fig. 1

Prostacyclin (PGI_2) possesses remarkable physiological activities including anti-hypertensive and platelet anti-aggregation effects.[6] However, PGI_2 with cyclic enol ether has a high sensitivity for hydrolysis, preventing its use as a therapeutic agent. Isocarbacyclin (9(*O*)-methano-$\Delta^{6(9\alpha)}$-PGI_1) (prostaglandin numbering), a carbacyclic analogue of PGI_2, overcomes this stability problem and still maintains sufficient physiological activity. As a result, isocarbacyclin presents a promising therapeutic agent for various thrombotic diseases.[5a,7] On the other hand, Δ^6-regioisomer (9(*O*)-methano-Δ^6-PGI_1) has only very weak physiological activity.[8] Thus, a regiochemical problem arises with respect to the introduction of a $\Delta^{6(9\alpha)}$ double bond. Our aim has been directed to the synthesis of isocarbacyclin analogues with a 2-allenyl side chain. Such an unsaturated functionality is crucial for a high biological activity in prostaglandin E analogues such as enprostil with 4-allenyl moiety and limaprost with 2-alkenyl moiety (Fig. 2).[5b]

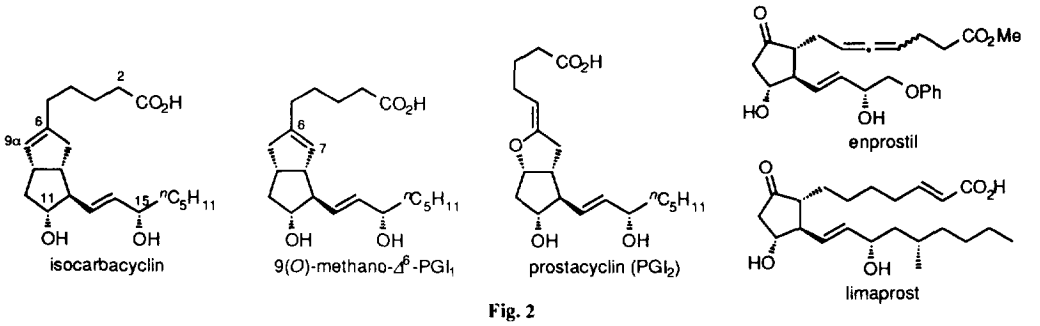


Fig. 2

Alkynylogous and vinylogous glyoxylates (**1** and **2**) were submitted to the asymmetric carbonyl-ene reaction with methylidenecyclopentane or -hexane in the presence of molecular sieves 4A in dichloromethane containing 20 mol% of the chiral BINOL-Ti catalyst, prepared from (*R*)-1,1'-bi-2-naphthol and diisopropoxytitanium dichloride as previously reported.[4] Standard work-up followed by column chromatography afforded the carbonyl-ene products (Table 1). High enantioselectivity was observed in each successive run. Significantly, alkynylogous glyoxylate **1** showed equally high reactivity and high enantiofacial selectivity to those shown by simple glyoxylate (entries 1-2 *vs.* 5-6).

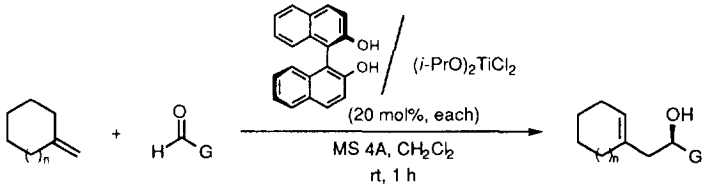
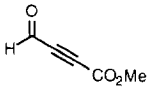
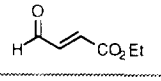
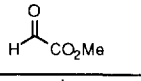


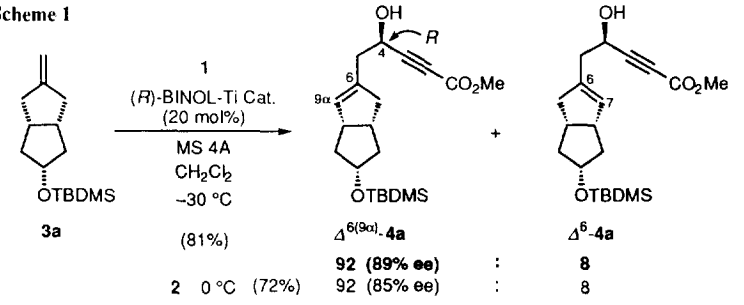
Table 1. Asymmetric Carbonyl-Ene Reactions Catalyzed by (*R*)-BINOL-Ti Complex.

entry	enophile	n	% yield[a]	% ee[b]
1		0	85	87
2		1	70	94
3		0	80	72
4		1	60	86
5[c]		0	93	88
6[c]		1	82	97

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis after conversion to corresponding (*R*)- and (*S*)-MTPA ester derivatives. [c] Reactions were performed at –30 °C (Ref. 4).

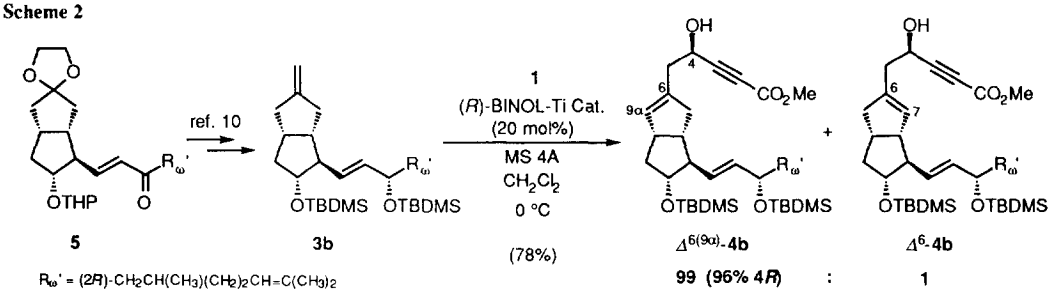
Next, asymmetric desymmetrization[9] of σ-symmetric prochiral bicyclic olefin **3a**[10] has been examined using this new type of catalytic asymmetric carbonyl-ene reaction as a model system for the synthesis of isocarbacyclin analogues (Scheme 1). The regioisomeric (diastereomeric) ratio ($\Delta^{6(9\alpha)}$-**4a** : Δ^{6}-**4a**) was determined by HPLC analysis. The enantiomeric purity and absolute stereochemistry of the major product (4*R*)-$\Delta^{6(9\alpha)}$-**4a** were determined by ^{1}H NMR (300 MHz) spectral analysis of the (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA ester) derivatives.[11] Thus, $\Delta^{6(9\alpha)}$-**4a** was obtained with high regio- and enantioselectivity using (*R*)-BINOL-Ti catalyst at a lower temperature.

Scheme 1



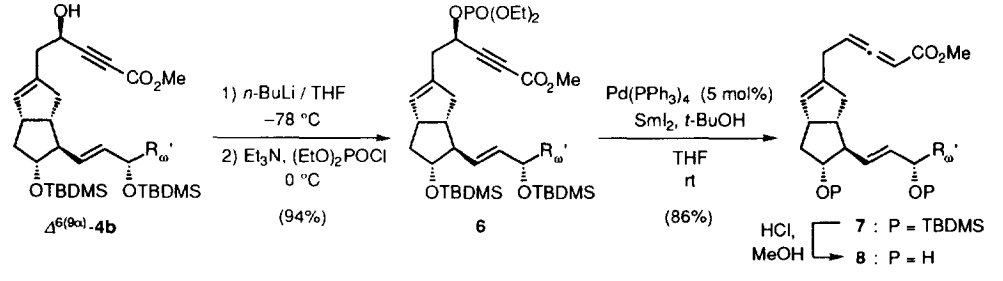
The double asymmetric[12] carbonyl-ene reaction with chiral bicyclic olefin **3b**[9] bearing an ω-side chain, catalyzed by (*R*)-BINOL-Ti, serves as a key step for the total synthesis of the potent analogues of isocarbacyclin. The enantio-pure intermediate **3b** was prepared from the known enone **5**.[13] As shown by the results of asymmetric desymmetrization of prochiral bicyclic olefin **3a**, the (*R*)-BINOL-Ti is considered to be better choice as a matched catalyst of choice for this enantio-pure ene component **3b** which bears the sterically demanding ω-side chain (Scheme 2). As a consequence, the double asymmetric induction by chiral bicyclic olefin **3b** and the (*R*)-BINOL-Ti catalyst led to the formation of the desired carbonyl-ene adduct **4b** in 99% $\Delta^{6(9\alpha)}$ regioselectivity, as determined by ^{1}H NMR and/or ^{1}H-^{1}H COSY analysis. The stereoselectivity at C_4 position was 96% *R* by LIS analysis using (+)-Eu(hfc)$_3$.[4]

Scheme 2



Further transformation of the propargylic alcohol functionality in the α-allenyl side chain is shown in Scheme 3. In this context, the present authors and Inanaga, *et al.* have already reported regioselective reduction of secondary propargylic phosphates to the allene derivatives using SmI_2, a catalytic amount of $Pd(PPh_3)_4$, and *tert*-butyl alcohol.[14] Thus, the ene adduct **4b** was converted *via* propargylic phosphate **6** to α-allenyl isocarbacyclin derivative **8** with extremely high regioselectivity in good yield.

Scheme 3



In summary, homologous glyoxylates (**1** and **2**) worked well as carbonyl enophiles in BINOL-Ti-catalyzed asymmetric ene reactions. The reaction using **1** was efficiently applied to the synthesis of α-allenyl isocarbacyclin analogue.

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