# Advances in catalytic, enantioselective aldol addition reactions with novel Ti(IV) complexes

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Global competition demands that new pharmaceuticals be prepared using cost-efficient and environmentally benign processes. The discovery and study of chemical reactions for applications in the synthesis of bioactive molecules is, therefore, of paramount importance. Advances in asymmetric catalysis should have an unquestionable impact on the development of chemotherapeutic agents. Here, the authors describe some recent developments from their laboratories in the general area of catalytic, enantioselective C–C bond-forming reactions.

The discovery and study of chemical reactions for applications in the synthesis of bioactive molecules is of paramount importance. Progress in human medicine is fueled by the availability of tailor-made compounds with designed physical or biological properties[1]. The resurgence of virulent strains of antibiotic-resistant pathogens has added additional impetus for the discovery and development of new chemotherapeutic agents. In living systems, drugs interact with molecular targets that are made up of chiral subunits (e.g. carbohydrates and amino acids) and, as a consequence, therapeutic agents are often themselves chiral. It is not uncommon to have desired medicinal properties of a drug associated with only one member of a stereoisomeric mixture of compounds. Moreover, in some instances, unwanted toxic side-effects result from stereoisomer contamination. Thus, in the preparation of chiral therapeutic compounds, it is important that the syntheses afford products of high optical purity[1,2].

Optically active pharmaceuticals constitute 20% of the top-selling drugs in the USA, and the worldwide market for chiral, nonracemic drugs has been estimated to exceed $35 billion[3]. Numerous technologies for asymmetric synthesis of such optically active molecules are available:

- Enzymatic or antibody catalysis[4,5];
- Use of optically active starting materials from the 'chiral pool', such as carbohydrates, amino acids, terpenes[6];
- Diastereoselective, chiral auxiliary-based synthesis methods[7]; and
- Metal-catalyzed, enantioselective synthesis[8–10].

Important examples of each of these technologies may be found in modern pharmacology at the various levels of discovery and development[11]. The use of metal-catalyzed enantioselective reaction processes for the synthesis of optically active molecules can offer advantages over more traditional methods; such synthetic transformations, utilizing substoichiometric quantities of a chiral reagent, are economically beneficial and environmentally benign[12].

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  1359-6446/96/$15.00 S1359-6446(96)10014-3 

Compounds containing the β-hydroxy carbonyl functionality and the corresponding reduced 1,3-diol subunits are ubiquitous in nature as secondary metabolites, which have been isolated from fungi, bacteria, animals, and plants (Figure 1). These include the polyene macrolide antibiotics, prostaglandins, compactin, and marine macrolides; all of which possess an equally varied spectrum of biological activity[13–15]. In addition, numerous man-made HMG-CoA reductase inhibitors incorporate the characteristic 1,3-functionality pattern[16]. One of the more efficient strategies for the construction of such fragments involves the aldol addition reaction of ketone or ester enolates with aldehydes (Figure 2). Such reaction methods, which combine C–C bond formation with concomitant installation of a chiral secondary alcohol, are powerful transformations in organic synthesis. We have been interested in the design, synthesis, and study of Lewis–acidic transition–metal complexes that function competently as catalysts for such carbonyl addition reactions[17–20]. This review focuses on recent results from our laboratories involving the preparation of chiral Ti(IV) complexes that catalyze the asymmetric addition of enol silanes and alkyl enol ethers with aldehydes. The optically active products isolated from these enantioselective reactions possess a β-hydroxy carbonyl functionality and serve as useful chiral starting materials for the synthesis of biologically active natural products and man-made molecules.

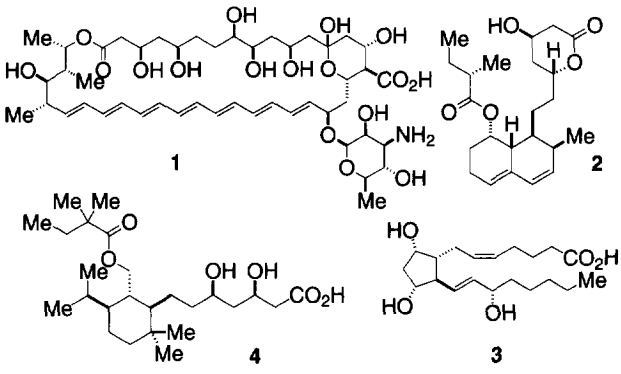



***Figure 1.*** *Bioactive molecules possessing 1,3-diol and β-hydroxy carbonyls. (a) Amphotericin B; (b) compactin; (c) HMG CoA inhibitor; (d) prostaglandin $F_{2\alpha}$.*

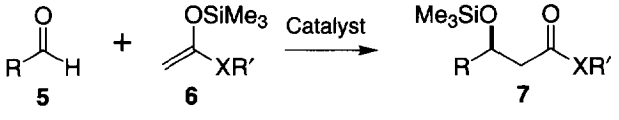


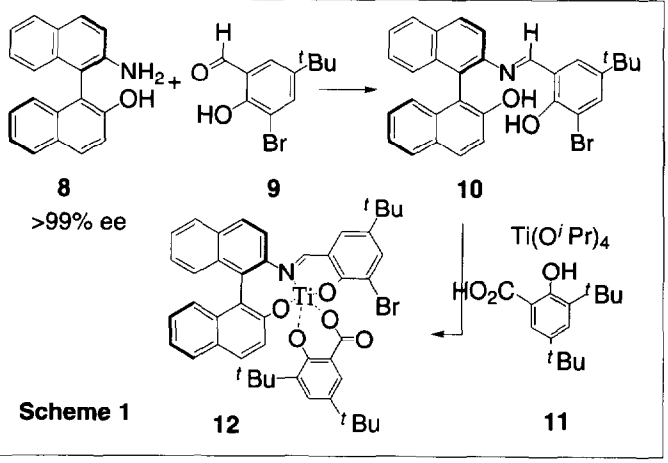

***Figure 2.*** *Aldol addition reaction of silyl enolates and aldehydes.*

Before discussing the specific catalytic, enantioselective processes that we have developed, it is important to delineate some of the important desirable features of any practical synthetic method. Reaction methodology applicable to a broad scope of substrates is highly valuable and provides access to a large family of structurally related molecules. The preceding statement may seem somewhat at odds with the fact that the results of extensive research involved in the drug discovery and development phases lead to the identification of a single compound with desired, optimized pharmacological properties. Indeed, an efficient, cost-effective synthetic process that leads to the production of such a compound would be deemed successful, even if it was singularly effective in providing the desired compound. However, the drug development process involves screening of numerous compounds, such that multiple pharmacological properties are simultaneously optimized. Thus, the drug design and discovery process is facilitated with reaction processes that display broad substrate tolerance.

Additional features are desirable for catalytic, enantioselective reaction methods. Ideally, it is important that such processes function at low catalyst loads and that the products of the reaction be isolated in high enantiomeric purity. Moreover, reaction processes that can be easily performed using low-cost, practical laboratory conditions are always preferable. We therefore set out to develop a catalytic aldehyde addition process that would furnish optically active β-hydroxy carbonyl compounds.

## Catalyst preparation

The results of some preliminary mechanistic investigations, together with the implementation of ligand design criteria, which are beyond the scope of this review, led us to identify complex **12** as a catalyst for a variety of aldehyde addition reactions (Scheme 1)21. The tridentate ligand with which the complex is prepared is readily obtained from (+)- or (–)-2-amino-2′-hydroxy-1,1′-binaphthyl **8** and 3-bromo-5-*tert*-butylsalicylaldehyde (**9**). Treatment of **10** with $Ti(O^iPr)_4$ and 3,5-di-*tert*-butyl-salicylic acid (**11**) affords an orange crystalline solid, which serves as the active catalyst. Although we do not yet have definitive data on the solution structure of the complex, we have found the structure shown for **12** may




Scheme 1

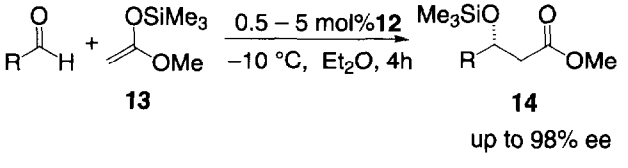



***Figure 3.*** *Catalytic, enantioselective aldol additions with the silyl ketene acetal derived from methyl acetate.*

be used as a working model to rationalize the results presented below.

## Additions with methyl acetate

The electron-rich *O*-silyl enol ether (**13**) derived from methyl acetate and $Me_3SiCl$ undergoes additions to aldehydes in the presence of as little as 0.5 mol % catalyst **12** to give optically active β-hydroxy ester adducts in high yields and up to 98% enantiomeric excess (ee) (Figure 3; Box 1)[22]. The reaction is tolerant of a wide range of substrates, such as aliphatic, aromatic and unsaturated aldehydes. Moreover, functionalized aldehydes can be successfully used to provide more complex adducts. Alkenyl and alkynyl aldehydes are particularly good substrates for this process, furnishing products consistently in high yields and selectivities. The extensive synthetic chemistry of propargyl and allylic alcohols makes the products isolated from this process particularly versatile starting materials for asymmetric synthesis.

We have performed studies aimed at establishing the general characteristics of the reaction process wherein reaction parameters, such as solvent, temperature and catalyst load, have been investigated. The reaction can be carried out in a variety of solvents, such as toluene, benzene, chloroform,

**Box 1. Representative aldehyde substrates with the corresponding adduct enantiomeric excess (ee)**

| Aldehyde | ee[a] |
|---|---|
| $Ph(CH_2)_3$—≡—CHO | 96% |
| $TBSOCH_2$—≡—CHO | 96% |
| Ph—≡—CHO | 94% |
| $^iPr_3Si$—≡—CHO | 97% |
| Me, CHO | 98% |
| Me, CHO | 95% |
| Ph, CHO | 98% |
| Ph, CHO | 94% |
| Me, PhCHO, $^tBuMe_2SiO$, CHO | 96% |
| | 95% |
| $^tBuPh_2SiO$, CHO | 91% |
| $Ph_3CS$, CHO | 98%[b] |
| $C_6H_{11}CHO$ | 95% |
| Me, CHO | 98% |
| Ph, CHO, Me | 95% |

[a]Aldol adducts isolated in pure form in 80–90% yield
[b]$Ph_3CS$-substituted aldehyde prepared and used as substrate in the aldol process by Dr J. Simon (Harvard University, Cambridge, MA, USA)

diethyl ether and *tert*-butyl methyl ether. Polar aprotic solvents, such as dichloromethane and dichloroethane, or Lewis basic solvents, such as tetrahydrofuran and acetonitrile, lead to significant reduction in the reaction enantioselectivity and cannot be employed. We have also observed that the addition reaction may be conveniently conducted between –20 to 23°C without adversely affecting the reaction rate (2–8 h) or enantioselectivity (>90%). For the aldol addition reaction of the methyl acetate derived silyl ketene acetal and aldehydes mediated by **12**, we have not observed diminution in the optical purity of the product throughout the catalyst range of 0.5–10.0 mol %.

### Acetoacetate additions

The aldol addition reaction methodology described herein can be employed in an iterative fashion to provide access to δ-hydroxy-β-keto esters (Scheme 2). However, application of the aldol process described above as well as other known aldol methods for the construction of δ-hydroxy-β-keto-esters and the derived 3,5-diol esters would require iterative carbonyl addition reactions with accompanying adjustments of oxidation states. Such sequential, iterative additions of acetate subunits parallel the natural polyacetate biosynthetic pathways (**15** → **17** → **18**). We envisioned that a more efficient synthetic strategy would utilize a four-carbon acetoacetate fragment **19** in the aldol addition reaction.

We have found that the silyl dienolate derived from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (diketene + acetone adduct) is an optimal four-carbon fragment (Figure 4). Dioxinone **20** is commercially available at a nominal price; in addition, the silyl dienolate **21** is readily prepared, purified by distillation, and stable to storage. The addition reactions of **21** with aldehydes were conducted with 1–3 mol % of catalyst **12** at 0°C (Figure 5; Box 2)[23]. A variety of aldehydes serve as substrates and yield aldol adducts in 79–97% yields. The absolute sense of induction parallels that which we have previously reported for the aldehyde additions of the methyl acetate-derived silyl enol ether. Some adducts are crystalline and as a consequence easily purified to high optical activity. For example, the cinnamaldehyde and benzaldehyde adducts (entries 3 and 5 in Box 2) were isolated in >99% ee (60% yield) and 96% ee (73% yield), respectively, after a single recrystallization.

The protected acetoacetate adducts are versatile precursors to optically active δ-hydroxy-β-keto esters, amides, and lactones (Scheme 3). For example, treatment of cinnamaldehyde adduct **22** with LiAl(NHBn)4 afforded crystalline amide **23** (73%); heating in n-BuOH converted **22** to ester **24**; in alkaline MeOH 22 yielded (79%) crystalline lactone **25**. The synthetic utility of adducts such as **23** and **24** is highlighted by the wealth of reaction methods that have been developed in industry and academia for their reduction to the corresponding *syn*- and *anti*-diols[24,25].

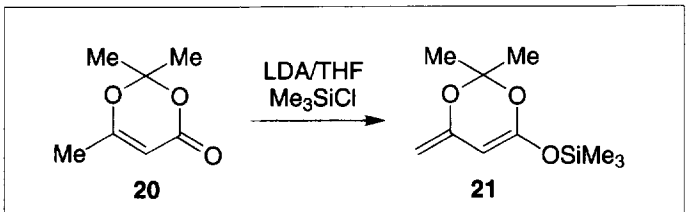



***Figure 4.*** *Preparation of the protected acetoacetate silyl dienolate.*

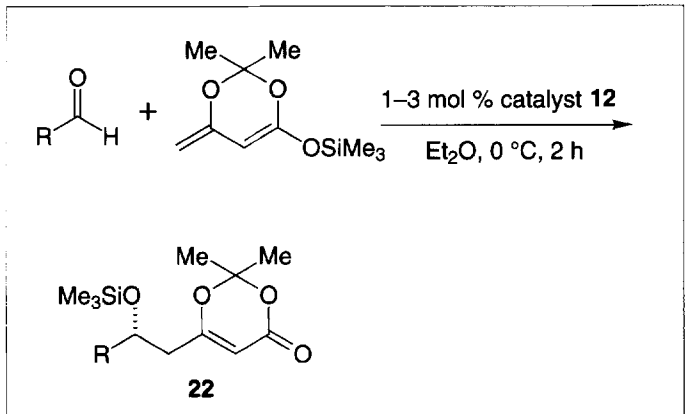
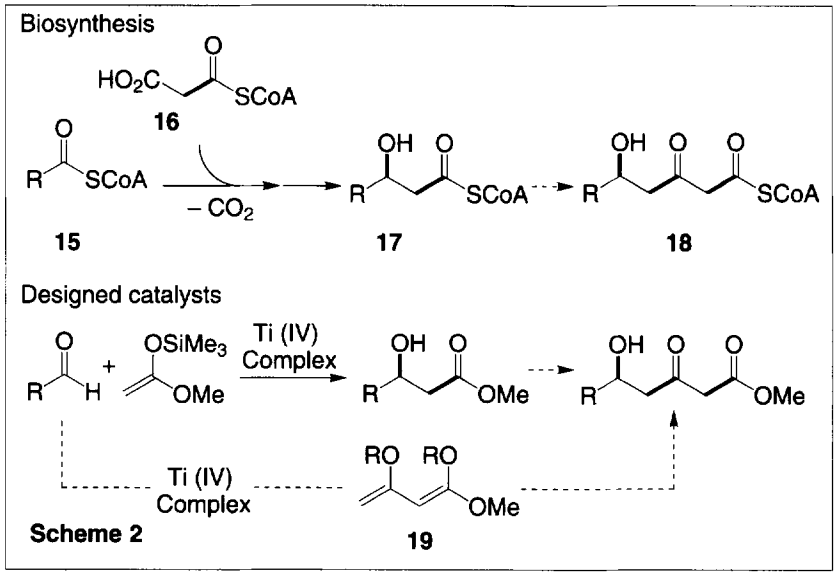



***Figure 5.*** *Catalytic, enantioselective acetoacetate additions.*

An application of the catalytic, enantioselective dienolate addition process that attests to the versatility of the reaction is illustrated in Scheme 4. We have recently demonstrated that the readily prepared stannyl propenal **26** is a substrate for the aldol addition. Thus, addition of **21** to **26** in the presence of 1 mol % catalyst 12 provides **27** in 92% enantiomeric excess (87% yield). This protected acetoacetate adduct **27** can be used as a versatile synthetic starting material which provides access to a library of functionalized δ-hydroxy-β-keto-esters. For example, coupling of the vinyl stannane **27** with aryl halides or triflates using $Pd^0$ chemistry affords a diverse

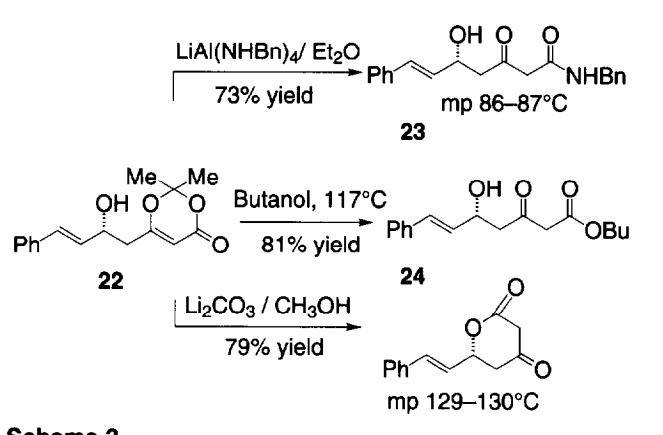



**Scheme 2**

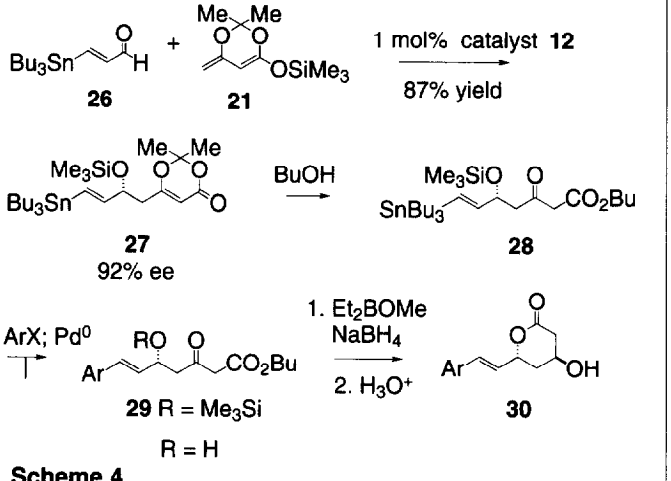
**Box 2. Additions of dienolate 21 to aldehydes**

| Entry | Aldehyde | ee |
|---|---|---|
| 1 | $^{i}Pr_3Si$—≡—CHO | 91% |
| 2 | $^{t}BuMe_2SiO$—CHO | 94% |
| 3 | Ph—CHO | 92% (99%)[a] |
| 4 | Me—CHO | 92% |
| 5 | PhCHO | 84% (96%)[a] |
| 6 | Ph—CHO | 80% |
| 7 | $Bu_3Sn$—CHO | 92% |

[a] Optical purity after a single recrystallization from hexane/ethyl acetate




**Scheme 3**




**Scheme 4**

array of aryl substituted acetoacetate adducts. Keto-esters **29** and related aryl-substituted analogs have been converted to medicinally important HMG-CoA reductase inhibitors **30** [26,27].

## Methoxypropene additions: preparation of acetone and hydroxyacetone adducts

The aldehyde addition reactions we have described rely on the use of ester *O*-silyl enol ether reagents. Although *O*-silyl enol ether derivatives of simple ketones (cyclohexanone, acetone) are commercially available, in general the corresponding ester derivatives (silyl ketene acetals) must be prepared in the laboratory prior to use and are sensitive to decomposition by moisture. As an alternative to the ester derived *O*-silyl ketene acetals, we have examined the inexpensive, commodity chemical 2-methoxypropene as an acetone enolate equivalent in catalytic, enantioselective aldehyde addition reactions[28]. We speculated that for such additions, which produce alcohol adducts directly, the use of the simpler chiral Ti(IV) complex **31** would suffice (Figure 6).

Under optimal conditions, the addition of 2-methoxypropene to aldehydes is conducted by dissolution of **31** (2–10 mol %) in 2-methoxypropene **32** (<$0.18/g) and addition of a hindered amine base and the substrate. Upon acidic work-up, β-hydroxyketone adducts are isolated (Figure 7). A variety of aldehydes serve as substrates in the addition reaction to yield acetone–aldol adducts in 79–99% yields and up to 98% ee (Box 3).

In the absence of an acidic work-up, the vinyl ether intermediates can be isolated, and these can be used in additional

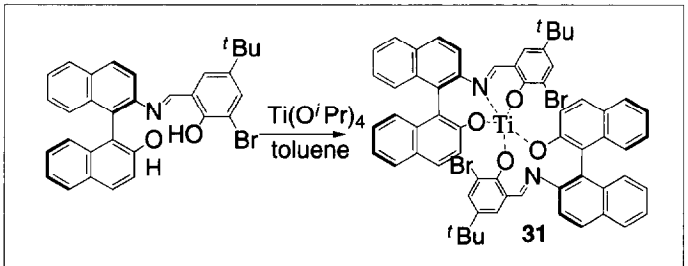



***Figure 6.*** *Preparation of the 2:1 Ligand–Ti complex.*

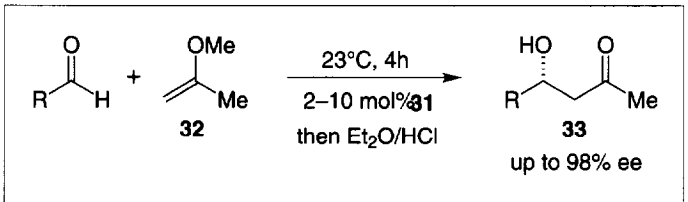
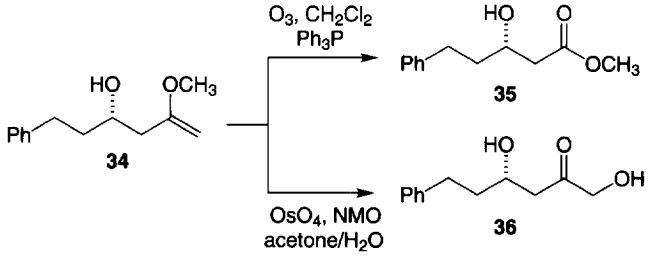



***Figure 7.*** *Aldehyde additions with the commodity chemical 2-methoxypropene.*




**Scheme 5**

**Box 3. Catalytic additions to aldehydes with 2-methoxypropene. ee, enantiomeric excess**

| Entry | Aldehyde | ee |
|---|---|---|
| 1 | $Ph(CH_2)_3$—≡—CHO | 98% |
| 2 | $TBSOCH_2$—≡—CHO | 93% |
| 3 | Ph—≡—CHO | 91% |
| 4 | Ph, CHO | 90% |
| 5 | PhCHO | 66% |
| 6 | $o$-$C_6H_{11}CHO$ | 75% |

synthetic transformations. For example, the adduct **34**, from the reaction of 2-methoxypropene and hydrocinnamaldehyde, was obtained in 84% yield after purification by chromatography on silica gel. Treatment of **34** with a dilute stream of ozone yielded β-hydroxyester **35** (Scheme 5); additionally, dihydroxylation of **34** (catalyst: $OsO_4$, NMO) furnished ketodiol **36**. Thus, as well as providing access to acetone aldol adducts (Box 3), the addition reactions employing 2-methoxypropene can also be used to prepare the corresponding optically active methyl acetate aldol adducts and more highly functionalized α′-hydroxyacetone adducts. This synthetic method constitutes a convenient alternative to the well-established aldol additions with enol silanes because 2-methoxypropene is readily available from commercial sources at low cost. Its use obviates the need for the laboratory preparation of the derived silyl enol ethers.

## Conclusion

The aldehyde addition processes described in this review highlight some recent developments in our laboratories in the general area of catalytic, enantioselective C–C bond-forming reactions. Important criteria that pertain to the design of practical catalytic systems have been noted; reaction parameters such as solvent, temperature, substrate scope and catalyst load should be given careful consideration because they are critical to the success of any reaction process. The catalytic enantioselective aldol addition reactions delineated herein in conjunction with other catalytic, asymmetric methods underscore the important discoveries that can be made in basic research at the interface of organic/inorganic synthesis and coordination chemistry. Global competition in the marketplace demands that new pharmaceuticals be prepared using cost-efficient and environmentally benign processes. Further advances in asymmetric catalysis should have an unquestionable impact on the development of chemotherapeutic agents for human medicine.

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