Alkynylzinc Addition

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Asymmetric Autocatalysis Enables an Improved Synthesis of Efavirenz**

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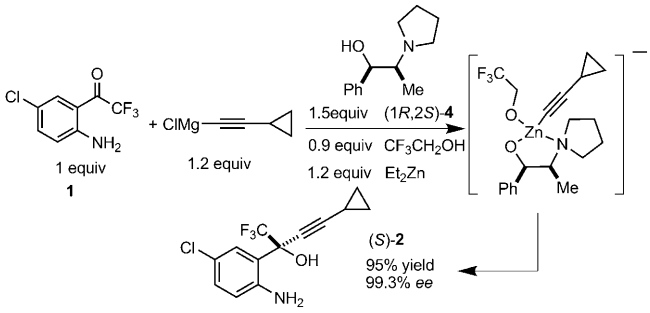
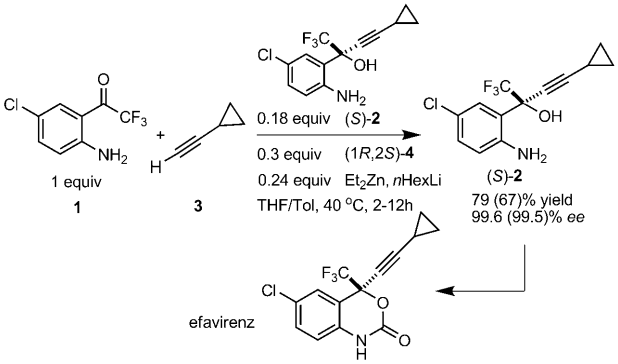
Asymmetric alkynylide additions to carbonyls have emerged as a useful tool in organic synthesis.[1] Several different stoichiometric and catalytic versions of additions to aldehydes have been documented for the preparation of secondary propargylic alcohols in high enantiomeric purity.[2] By contrast, enantioselective alkynylation of ketones towards the formation of tertiary alcohols has enjoyed only limited success with respect to both scope and selectivity.[3] Unquestionably, the most prominent example of zinc-mediated asymmetric alkynylation of ketones was described by Tan and co-workers at Merck for the manufacture of efavirenz[4] (Sustiva, Stocrin), a key drug for the treatment of HIV.[5a,b] This landmark chemical process prescribes the use of stoichiometric quantities of diethylzinc, metalated acetylene, chiral amino alcohol ligand, and trifluoroethanol additive to furnish the key intermediate (*S*)-**2** in 99.3 % *ee* and 95 % yield (Scheme 1).[5c] Herein, we disclose a catalytic, enantioselective process, which involves the use of a cocktail including substoichiometric quantities of the ligand (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine (**4**),[6] Et_2Zn, and substoichiometric amounts of the product (*S*)-**2** at the outset of the reaction.[7] The catalytic reaction benefits from the presence of product as an autocatalyst, resulting in a more atom-economical route to efavirenz in 79(67) % yield and 99.6(99.5 %) % *ee*.[8]



Scheme 1. Current "stoichiometric" synthesis of (*S*)-**2**, a key intermediate in the synthesis of efavirenz.

Beyond the economic relevance, this process showcases the first example that employs autocatalysis in the synthesis of a pharmaceutical agent which may be conducted on large scale (Scheme 2).[9]



Scheme 2. Enantioselective synthesis of efavirenz by means of the autocatalytic formation of the key intermediate (*S*)-**2**.

We have been interested in the chemistry of terminal acetylenes in catalytic, enantioselective synthesis.[2j–n] Because of the global importance of efavirenz for human health, we turned our attention to its synthesis. The current large-scale production of the key intermediate (*S*)-**2** proceeds through a chiral zincate, requiring excess quantities of the chirality-inducing ligand **4** (1.5 equiv), 1.2 equiv of Et_2Zn, and 0.9 equiv of trifluoroethanol (Scheme 1).[10] We set out to carefully examine this process with the aim of establishing a cost-effective protocol that would employ substoichiometric amounts of these components, namely a catalytic enantioselective process.[11]

Given the regulatory and financial issues involved in registering a new protocol for an existing drug, we set out to craft a catalytic, enantioselective process that would parallel the current stoichiometric one. We thus focused our efforts on the screening of reaction parameters, such as base, temperature, concentration, solvent polarity, order of addition of the various components, and relative proportions of the components. In our initial studies the most promising result was achieved with 0.3 equiv of (1*R*,2*S*)-**4**, 0.24 equiv of Et_2Zn, 0.18 equiv of CF_3CH_2OH, 0.8 equiv of Li*O*t*Bu* as the base, and 1.1 equiv of cyclopropyl acetylene **3**. Under these conditions the desired tertiary alkynol (*S*)-**2** was formed with 97.4 % *ee* and 40.4 % yield, based on the HPLC analysis of the reaction aliquot after 4 h at 23 °C. This outcome suggested that the system might exhibit turnover, but further

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optimization was required. Extensive screening of a number of parameters including achiral additives ($(CF_3)_2CHOH$, $CF_3(CH_3)CHOH$, $(CH_3)_3COH$, $C_6H_5CH(CF_3)OH$, *t*BuOH), dialkylzinc reagents (Me_2Zn, Ph_2Zn), and bases for alkyne deprotonation (LiOTMS, KOTMS, KO*t*Bu, CsOH, Et_3N, pyridine, CF_3CH_2OLi, *n*BuLi) resulted in either poor yields or low enantioselectivity, thus, forcing us to embark on the examination of less obvious parameters. Analogous investigations of these parameters had been reported by Grabowski for the addition of alkynyl Grignard reagents without any notable success as well.[10]

The first systematic study on the effect of an enantiomerically enriched product acting as a ligand in an intermediate complex in an asymmetric reaction was carried out by Alberts and Wynberg.[12,13] Pioneering studies by Soai have highlighted important observations concerning autocatalysis in enantioselective alkylzinc additions, involving the addition of iPr_2Zn to substituted 2-pyrimidine carboxaldehydes.[14] A key lesson from this specific work is the ability of the reaction product to effect its own synthesis in high enantiomeric purity. Although the potential importance of this process to the question of the origin of chirality has been considered and scrutinized, its application in preparative chemistry and in particular to the manufacture of a pharmacologically active ingredient has, to the best of our knowledge, gone unreported. Moreover, autocatalysis in the enantioselective alkynylation of ketones has, to the best of our knowledge, not been previously noted.

We embarked on a series of studies aimed at examining autoinduction by the product in developing a catalytic, enantioselective approach to (*S*)-**2**. Having product alkynol (*S*)-**2** in its enantiomerically pure form at our disposal, we conducted a set of experiments which afforded promising initial results. Thus, when 0.3 equiv of (1*R*,2*S*)-**4**, 0.24 equiv of Et_2Zn, and 0.18 equiv of (*S*)-**2** were employed with *n*BuLi as the base, the desired product was formed in 52% yield and 86% *ee* after 18.5 h at room temperature (Table 1, entry 1).[15] Next, we observed that the system was robust even when subjected to heating[16] and that employing *n*HexLi instead of *n*BuLi to effect alkyne deprotonation was beneficial (Table 1, entry 2). The modest yield could be attributed to partial dimerization of the substrate during the course of the reaction.[17]

In a study by Cozzi et al. involving methyl alkynylzinc additions to ketones, the carbonyl substrate itself was implicated as a ligand that facilitates the zinc-mediated addition of alkynes to the substrate,[18] thus implicating a putative, competitive stereorandom background reaction. To ensure a sustained low concentration of **1**, it was added slowly and simultaneously with *n*HexLi.[19] These conditions along with heating proved optimal and led to further increase in the yield (87%) and enantiomeric excess (90% *ee*) of the isolated product (Table 1, entry 3). A larger-scale preparative experiment (250 mmol) under otherwise identical conditions afforded product in good yield and 99.6% *ee* (Table 1, entry 4).[20] Nearly the same product yield and enantiomeric purity were observed with longer reaction time upon twofold decrease in the amount of product autocatalyst (Table 1, entry 5 versus entry 3). It is important and surprising to note

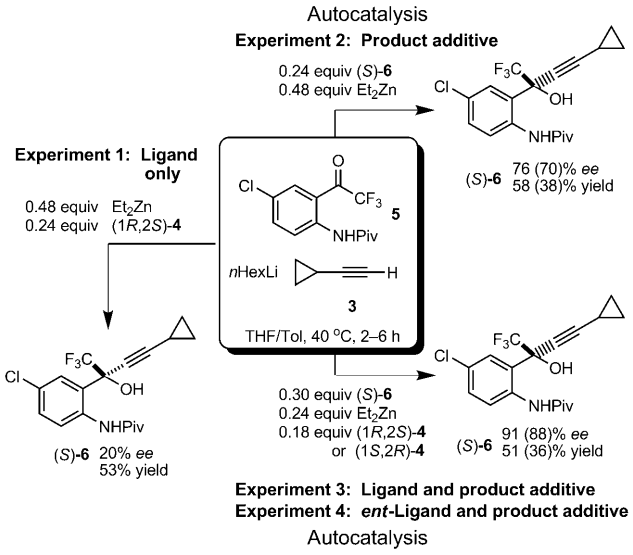
Table 1: Study of addition reactions of **3** to **1** (Scheme 2).

Entry	**4** [mol%]	(*S*)-**2** [mol%]	*T* [°C]	*t* [h]	Product (*S*)-**2** yield [%][a]	*ee* [%][b]
1[c,f]	30	18	25	18.5	52(37)[h]	86(80)
2[c]	30	18	40	6.5	83(68)[h]	85(81)
3[c,k]	30	18	40	2	87(69)[g]	90(88)
4[c,d,k]	30	18	40	12	79(67)[l]	99.6(99.5)
5[c,k]	39	9	40	6	85(76)[g]	87(85)
6[e,k]	–	24	25	1.5	81(61)[h]	rac
7[c,i,k]	30	18	40	3	91(76)	39(67)[j]

[a] Yields after subtraction of the initially added product are given in parentheses. [b] *ee* values were determined by HPLC with a Daicel Chiralpak AD-H column, hexanes/*i*PrOH 85:15, 1 mL min^{-1}. Values corrected for initially added (*S*)-**2** ligand are given in parentheses (see Ref. [15]). [c] Performed with (1*R*,2*S*)-**4** unless otherwise stated, 2 mmol scale, THF(major component)/Tol/hexanes, 0.24 equiv of Et_2Zn, 0.9 equiv of *n*HexLi, 2 equiv of **3**. [d] 250 mmol scale, identical to conditions in [c]. [e] 2 mmol scale, toluene as a major solvent component (see Ref. [21a]), 0.48 equiv of Et_2Zn, 1 equiv of *n*HexLi, 2 equiv of **3**. [f] 2 equiv of *n*BuLi as a base. [g] Yield of isolated product after purification by chromatography. [h] Product was not isolated; yield was calculated by HPLC analysis of the reaction aliquot. [i] Performed with (1*S*,2*R*)-**4**. [j] *ee* of (*R*)-**2**. [k] Slow simultaneous addition of *n*HexLi and aminoketone **1** to the reaction mixture. [l] Yield of isolated product after crystallization.[20]

that in the absence of the external ligand (1*R*,2*S*)-**4** the product is formed as a racemate (Table 1, entry 6).[21] Thus the autocatalytic effect in this process is rather special, requiring **4** as a second chiral component or ligand.

We decided to examine addition reactions of the *N*-pivaloyl-protected derivative (*S*)-**6** (Scheme 3). In the first experiment, the addition of **3** to **5** mediated by 0.24 equiv of ligand **4** afforded product (*S*)-**6** in 20% *ee* (Table 2, entry 1). Thus, in contrast to additions to **1**, use of ligand alone gives very poor conversion and asymmetric induction. In a second set of investigations, when the addition was carried with 0.24 equiv of added product as autocatalyst,



Scheme 3. Addition of alkyne **3** to *N*-pivaloyl-protected **5**.

Table 2: Study of addition reactions of **3** to **5** (Scheme 3).

Entry	**4** [mol%]	(*S*)-**6** [mol%]	*T* [°C]	*t* [h]	Product (*S*)-**6** yield [%][a]	*ee* [%][b]
1[c,d]	24	–	40	7	53[f]	20
2[c,d]	–	24	40	2	58(38)[e]	76(70)
3[c]	18	30	40	6	51(36)[e]	91(88)
4[c,g]	18	30	40	2	49(30)[e]	94(92)

[a] Yields after subtraction of the initially added product are given in parentheses. [b] *ee* values were determined by HPLC with a Daicel Chiralpak AD-H column, hexanes/*i*PrOH 85:15, 1 mL min^{-1}. Values corrected for initially added (*S*)-**6** ligand are given in parentheses (see Ref. [15]). [c] Performed with (1*R*,2*S*)-**4** unless otherwise stated, 2 mmol scale, THF(major component)/Tol/hexanes, 0.24 equiv of Et_2Zn, 0.9 equiv of *n*HexLi, 2 equiv of **3**. [d] 0.48 equiv of Et_2Zn. [e] Yield of isolated product after purification by chromatography. [f] Product was not isolated; yield was calculated by HPLC analysis of the reaction aliquot. [g] Performed with (1*S*,2*R*)-**4**.

but no ligand **4**, the alcohol adduct (*S*)-**6** was obtained in 58% yield and 76% *ee* (Table 2, entry 2).[22] This finding is intriguing, because, unlike (*S*)-**2**, the product as a chiral controlling group is dominant over ligand **4** in promoting the reaction and dictating the configuration of the newly formed product (*S*)-**6** (compare with Table 1, entry 6). In a third experiment, when the addition was conducted in the presence of both ligand **4** and the autocatalyst product ((*S*)-**6**/(1*R*,2*S*)-**4** 0.3:0.18), (*S*)-**6** adduct was isolated in 51% yield and 91% *ee* (Table 2, entry 3).[23]

Finally, a fourth experiment was carried out to examine whether there was a matched and mismatched pair of combinations involving (1*S*,2*R*)-**4**, (1*R*,2*S*)-**4**, and (*S*)-**6**. Surprisingly, the analysis of the reactions indicated enantioselective formation of (*S*)-**6** regardless of the amino alcohol ligand employed (Table 2, entries 3 and 4).[24] This dominant effect of product as an autocatalyst which dictates the absolute configuration of the adduct **6** was not detected in the case of (*S*)-**2** (Table 1, entry 7). Consequently, the configuration of the product autocatalyst is crucial for asymmetric induction in this transformation.[25] Although the enantioselectivity and yield were only moderate, this system exhibits the very first example of an asymmetric autocatalytic alkynylation of a ketone, where the product constitutes the only source of chiral catalyst (Table 2, entry 2).

The origin of the enantiofacial bias in asymmetric zinc alkylation reactions mediated by rigid bidentate β-aminoalcohols is well described by the Noyori–Kitamura five-ring chelate model.[26] The enantioselective addition of lithium acetylide–ephedrate to the PMB-protected aminoketone **1** (PMB = *p*-methoxybenzyl) was accounted for by the active 2:2 cubic tetramer, which was well characterized by spectroscopic and structural methods.[27] By contrast, reliable mechanistic studies on 1,2-alkynylzinc additions, in particular catalytic reactions, are lacking. We have obtained a crystal structure of a complex formed by Et_2Zn, **4**, and **6**, which is competent as a catalyst, albeit with reduced selectivity, and is instructive to examine (see the Supporting Information). However, at present a detailed construct to rationalize the autocatalytic effects we observed must await additional in-depth mechanistic studies. Nonetheless, the phenomenological autocatalytic effect of the product can become beneficial in the catalytic, enantioselective synthesis of important pharmaceutical intermediates. The possibility of the practical application of this autocatalysis concept, which is otherwise largely of academic significance, is to the best of our knowledge unprecedented.

In summary, we have documented a catalytic enantioselective process for the production of a key precursor to efavirenz. Key to the development was the use of the product as an inherent part of the catalytic system. This novel approach towards zinc acetylide addition to ketones expands the arsenal of existing autocatalytic transformations and also poses general challenging questions about the product's role in asymmetric reactions. In a manner that is complementary to Soai's involving autocatalysis, the strategy described herein has demonstrated the conversion of a catalytic, enantioselective transformation, which is poorly selective even in the presence of an external chiral catalyst, into a highly selective process. It also provides an example wherein the presence of the product as well as a second chiral catalyst can work in synergy to generate a catalytic and enantioselective reaction process. Following the strategy outlined, we believe the manufacturing cost of efavirenz could be substantially reduced in comparison to this of the existing stoichiometric process. There has been considerable public debate on the affordability of medicines; in this respect the approach we describe may provide wider access to therapy to patients worldwide. Additionally, we believe that this is fertile territory for future explorations in the field.

Experimental Section

General experimental procedure and characterization of the propargylic alcohols, as well as spectroscopic data of the discussed compounds can be found in the Supporting Information. CCDC-652045 and 652046 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[8] The numbers in the parentheses represent the yield and the *ee* values obtained after the subtraction of the initially added product (*S*)-**2**. See Ref. [15] for the detailed calculations.

[9] We coin the term "semi-autocatalysis" implying the necessity of an external enantiomerically pure ligand in addition to the product itself in order to attain acceptable values for *ee* and conversion.

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[15] To assess the inherent asymmetric induction in the various experiments, the *ee* of the newly formed product (ee_p) was corrected for the presence of the optically active product at the outset as follows: a) From the HPLC chromatogram of a reaction aliquot (since the *ee* of the initial self-catalyst in all cases is > 99.99%, it is rounded to 100% for simplicity): $ee_p = \{[S-A(n_0/(n_S+n_0))-R]/[S-A(n_0/(n_S+n_0))+R]\}\cdot 100\,\%$, where S = total peak area of the initial and newly formed *S* enantiomer, A = total peak area of the substrate, the product, and side products, R = peak area of the newly formed *R* enantiomer; n_S = substrate [mmol], n_0 = product initially added [mmol]; b) For the isolated product: $ee_p = (n_1/(n_1-n_0))\cdot(ee_p'-(n_0\,100/n_1))$, where n_1 = isolated product [mmol], n_0 = product initially added [mmol], ee_p' = observed *ee* of the isolated product (see Ref. [13g]); c) Optionally, the *ee* of the isolated product is defined as follows: from the crude mixture the ratio $S_{new}/S_0 = [S-A(n_0/(n_S+n_0))]/[A(n_0/(n_S+n_0)]$ is calculated, where S_{new} = peak area of the newly formed *S* product, S_0 = peak area of the initially added *S* product, S = total peak area of the initial and newly formed *S* product, A = total peak area of the crude mixture, n_0 = product initially added [mmol], n_S = substrate [mmol]. The ratio is then substituted to the $S = S_{new} + S_0$, where S = total peak area of the isolated *S* product. Once S_{new} is found, the $ee_p = [(S_{new}-R)/(S_{new}+R)]\,100\,\%$.

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[20] This process afforded 97.4% yield and 94% *ee* after 12 h according to the HPLC chromatogram of the reaction aliquot (see the Supporting Information). The yield drop (79%) along with the *ee* increase (99.6%) apparently occurred during the purification step, which furnished the product (*S*)-**2** as a methanesulfonic acid salt. The crystallization was performed according to the current industrial method (C. Y. Chen (Merk), WO-9911600, **1999**). The product in entries 3 and 5 (Table 1) was purified by column chromatography on silica gel thus affording higher yields.

[21] a) An autocatalytic process (with **2** and no (1*R*,2*S*)-**4**) was performed in toluene at room temperature to prevent the cyclization of the obtained product into quinoline (B. Jiang, Y.-G. Si, *J. Org. Chem.* **2002**, *67*, 9449 – 94519); b) It is worth mentioning that autostereoamplification was attempted in the past employing lithium acetylide addition to **1**. The authors reported using lithiated (*S*)-**2** in lieu of (1*R*,2*S*)-**4**, which afforded 70% *ee* favoring the wrong enantiomer. A reduction in the stoichiometry of the chiral ligand was reported in the same work, achieving a 1:0.5 ratio for **1**/(1*R*,2*S*)-**4** by recycling process. However, the *ee* value dropped from > 98% to 90.8%, placing a practical limit on this approach. A. Choudhury, J. R. Moore, M. E. Pierce, J. M. Fortunak, I. Valvis, P. N. Confalone, *Org. Process Res. Dev.* **2003**, *7*, 324 – 328.

[22] In Ref. [13a–f] the product is described as an inherent (yet, not exclusive) part of a catalytic species. However, Soai's reports

leading to the formation of secondary alcohols and asymmetric Mannich reactions (Ref. [13g]) are examples where the product is the only (and sufficient) chiral inductor.

[23] As the reaction failed to proceed to completion, thus unreacted starting material could be retrieved in all experiments.

[24] Soai et al. have described similar observations related to their autocatalytic system involving aldehyde additions: a mixture of two competing pro-*S* and pro-*R* ligands afforded highly enantioenriched product, implying one ligand far outweighs another in its ability of enantiofacial control: K. Soai, I. Sato, F. Lutz, *Org. Lett.* **2004**, *6*, 1613 – 1616.

[25] It is noteworthy that PMB-protected **1**, submitted to the same transformation (i.e., (1*R*,2*S*)-**4** and PMB-protected (*S*)-**2** as catalysts), exhibited no enantiofacial differentiation, affording completely racemic product in nearly quantitative yield (determined by GCMS on a chiral stationary phase). This finding differs radically from the highly selective lithium acetylide alkynylation of PMB-protected **1**, performed with (1*R*,2*S*)-**4**—the key step in the lithium-assisted manufacture of efavirenz (see Ref. [27a,b]).

[26] For the earliest works see: a) R. Noyori, S. Suga, K. Kawai, S. Okada, M. Kitamura, *Pure Appl. Chem.* **1988**, *60*, 1597 – 1606; b) R. Noyori, S. Suga, S. Okada, M. Kitamura, *J. Am. Chem. Soc.* **1989**, *111*, 4028 – 4036; c) R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *109*, 34 – 55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49 – 69.

[27] a) A. S. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 8937 – 8940; b) M. E. Pierce, R. L. Parsons, Jr., L. A. Radesca, Y. S. Lo, S. Silverman, J. R. Moore, Q. Islam, A. Choudhury, J. M. D. Fortunak, D. Nguyen, C. Luo, S. J. Morgan, W. P. Davis, P. N. Confalone, C. Y. Chen, R. D. Tillyer, L. Frey, L. Tan, F. Xu, D. Zhao, A. S. Thompson, E. G. Corley, E. J. J. Grabowski, R. Reamer, P. J. Reider, *J. Org. Chem.* **1998**, *63*, 8536 – 8543; c) A. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowski, J. F. Remenar, D. B. Collum, *J. Am. Chem. Soc.* **1998**, *120*, 2028 – 2038; d) F. Xu, R. A. Reamer, R. Tillyer, J. M. Cummins, E. J. J. Grabowski, P. J. Reider, D. B. Collum, J. C. Huffman, *J. Am. Chem. Soc.* **2000**, *122*, 11112 – 11118; e) X. Sun, M. D. Winemiller, B. Xiang, D. B. Collum, *J. Am. Chem. Soc.* **2001**, *123*, 8039 – 8046.

