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Asymmetric autocatalysis of a ferrocene-containing chiral compound with amplification of chirality

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Dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—Chiral ferrocene-containing pyrimidyl alkanol can be efficiently synthesized via asymmetric autocatalysis as an enantiomerically pure product. Moreover, a remarkable positive nonlinear effect occurs during this autocatalytic reaction. Starting from a nearly racemic seed, it is thus possible to produce a larger amount of the same compound with high ee.

1. Introduction

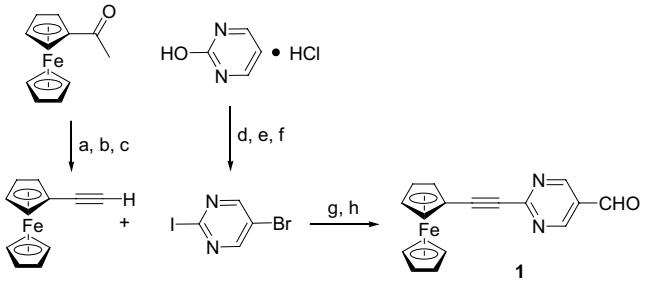
Since the discovery of ferrocene,[1] a large number of derivatives have been prepared and offered great applications in diversified fields of research.[2] For example, the physical properties (e.g., optical, electrical, magnetic, and redox activity) of ferrocene derivatives have been used in electronic sensors, electrochemical agents, liquid crystals, and molecular ferromagnets.[3] On the other hand, its unique structural and chemical properties have also brought applications in asymmetric catalysis[4] and even in medicine.[5] In particular, alkynylferrocene was shown to be a useful synthon for material sciences, and its conjugated and rigid structure offers promising properties in nonlinear optics.[6]

On the other hand, during our studies on the enantioselective addition of dialkylzincs to aldehydes,[7] we discovered that some of these reactions are autocatalytic, that is, the chiral product acts as a chiral catalyst for its own production.[8,9] Moreover, among these autocatalytic systems, an amplification of enantiomeric excess (ee) occurs and the final product has the same structure and absolute configuration as the catalyst, but has a higher ee.[8a,c] In particular, the autocatalytic ability of various (2-alkynyl-5-pyrimidyl)alkanols was shown to strongly depend on the electron-withdrawing effect and the suitable bulkiness of the alkyne moiety of the autocatalyst.[8b]

As combining the physical particularities of ferrocene and the unique autocatalytic properties of pyrimidyl alkanols may lead to interesting features, the possibilities of asymmetric autocatalysis of ferrocene-containing pyrimidyl alkanol were envisaged.

2. Results and discussion

2-Ferrocenylethynylpyrimidine-5-carboxaldehyde **1** was easily synthesized in a convergent manner from commercially available acetylferrocene and 2-hydroxypyrimidine with a 57% overall yield (Scheme 1).[8b,10]



Scheme 1. Synthesis of 2-ferrocenylethynylpyrimidine-5-carboxaldehyde **1**. Reagents and conditions: (a) LDA, THF, −78 °C; (b) $ClPO(OEt)_2$, −78 °C to rt; (c) LDA, −78 °C to rt, 77% over three steps; (d) Br_2, H_2O; (e) $POCl_3$, $PhNMe_2$, 86% over two steps; (f) 57% HI, CH_2Cl_2, 0 °C, 91%; (g) 1 mol % $Pd(PPh_3)_4$, 2 mol % CuI, *i*-Pr_2NH, THF, 0 °C, 92%; (h) *n*-BuLi, THF, −100 °C, then HCO_2Et, 81%.

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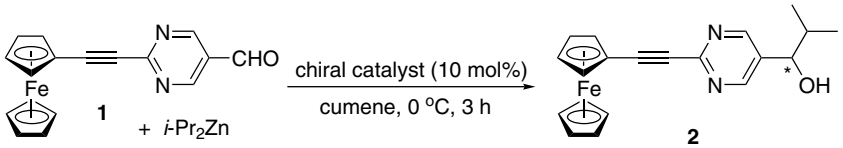
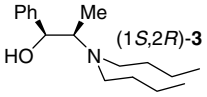
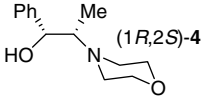
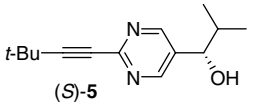
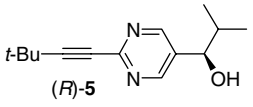
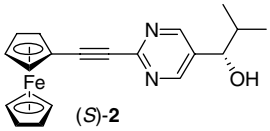
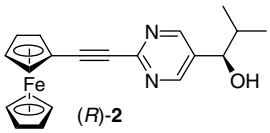
2-(Ferrocenylethynyl-5-pyrimidyl)-2-alkanol **2** can be obtained with high enantioselectivity by common asymmetric catalysis and by asymmetric autocatalysis. The results are shown in Table 1. Thus, when the addition of diisopropylzinc to 2-ferrocenylethynylpyrimidine-5-carboxaldehyde **1** was performed in cumene in the presence of a catalytic amount (10 mol %) of (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (DBNE **3**),[11] (*S*)-alkanol **2** was obtained with high yield (95%) and high ee (98% ee, entry 1). Conversely, (*R*)-alkanol **2** with 98% ee was obtained by using (1*R*,2*S*)-2-morpholino-1-phenylpropanol (MPP **4**)[11c] as a chiral catalyst (entry 2). A more efficient catalytic transfer of chirality could be obtained in a pseudo-autocatalytic manner. Thus, by using enantiomerically pure 1-(2-*tert*-butylethynyl-5-pyrimidyl)-2-methylpropan-1-ol **5** as catalyst of the reaction,[8b,c,12] alkanol **2** was obtained in a practically enantiopure form (>99% ee) (entries 3 and 4). As the chiral catalyst and chiral product bear different alkynyl moieties, these reactions are not strictly autocatalytic; however, such a high level of enantioselectivity that can be reached may be linked with the structural similarities of the aldehyde and catalyst.

Enantiopure alkanol **2** was then used as a chiral catalyst for its own formation to estimate the autocatalytic properties of this compound (entries 5 and 6). The resulting products **2** of these autocatalytic reactions were also enantiomerically pure (>99% ee) and obtained in high yields (95 and 97%).[13] These reactions can easily be monitored by the change in color, as aldehyde **1** is purple, whereas alkanol **2** (and its zinc alkoxide) is orange. Thus, asymmetric autocatalysis of 2-(ferrocenylethynyl-5-pyrimidyl)-2-alkanol **2** proceeds with even higher enantioselectivity than conventional asymmetric catalysis.

The possibility of asymmetric amplification during autocatalytic formation of 2-(ferrocenylethynyl-5-pyrimidyl)-2-alkanol **2** was then estimated by using (*S*)-**2** with a low ee as a catalyst for the addition of diisopropylzinc to aldehyde **1** in toluene (Table 2). By using 10 mol % of (*S*)-**2** with 8% ee as an autocatalyst, (*S*)-alkanol **2** was obtained with an enhanced enantiopurity of 67% ee (entry 1). Considering that this product obtained includes the initial autocatalyst; this means that the newly formed (*S*)-**2** was produced with 73% ee in 85% yield.

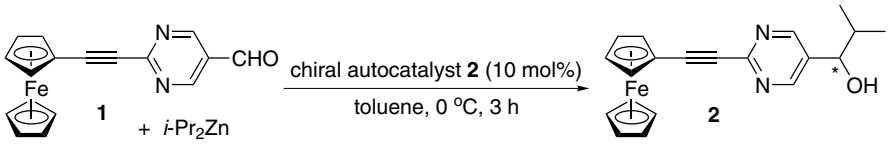
Table 1. Enantioselective synthesis by asymmetric catalysis or asymmetric autocatalysis



Entry	Chiral catalyst[a]	Alkanol **2**	
		Yield (%)	ee (%)[b]
1	 (1*S*,2*R*)-**3**	95	98 (*S*)
2	 (1*R*,2*S*)-**4**	92	98 (*R*)
3	 (*S*)-**5**	92	>99 (*S*)
4	 (*R*)-**5**	90	>99 (*R*)
5[c]	 (*S*)-**2**	97	>99 (*S*)
6[c]	 (*R*)-**2**	95	>99 (*R*)

[a] Enantiomerically pure chiral catalysts were used.
[b] Determined by HPLC using a chiral stationary phase (Chiralcel OD-H).
[c] Autocatalytic reactions.

Table 2. Asymmetric amplification by asymmetric autocatalysis



Entry[a]	Set[b]	Initial ee of the autocatalyst **2** (%)	ee of the isolated **2** after reaction (%)	Newly formed alkanol **2**	
				Yield (%)	ee (%)
1	A	8 (*S*)	67 (*S*)	85	73 (*S*)
2	A	67 (*S*)	77 (*S*)	69	78 (*S*)
3	A	77 (*S*)	88 (*S*)	83	90 (*S*)
4	A	88 (*S*)	94 (*S*)	88	94 (*S*)
5	B	8 (*R*)	66 (*R*)	79	72 (*R*)
6	B	66 (*R*)	74 (*R*)	72	75 (*R*)
7	B	74 (*R*)	88 (*R*)	96	89 (*R*)
8	B	88 (*R*)	90 (*R*)	86	90 (*R*)

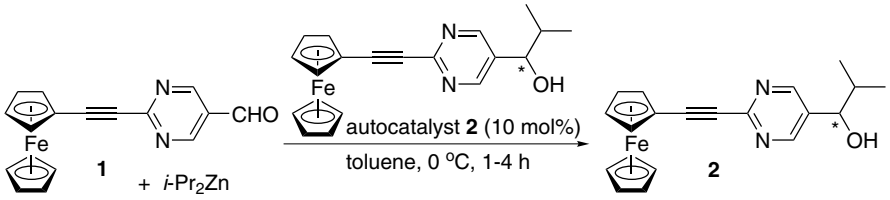
[a] Molar ratios of asymmetric autocatalyst **2**: aldehyde **1**:*i*-Pr_2Zn = 0.1:1:2.4.
[b] Starting autocatalysts (*S*)- and (*R*)-**2** with low ee (entries 1 and 5) were prepared by mixing enantiomerically pure and racemic **2**.

By taking advantage of asymmetric autocatalysis, the alkanol obtained (*S*)-**2** can in turn be used as an autocatalyst, and after four consecutive cycles, (*S*)-**2** with 94% ee was obtained (entries 2–4, set A). Similarly, starting from a catalytic seed of (*R*)-**2** with only 8% ee, alkanol (*R*)-**2** with 90% ee has been produced with high yield after 4 consecutive asymmetric autocatalyses (entries 5–8, set B).

Thus, as shown in Table 2, the slight imbalance of enantiomers in the initial autocatalyst **2** (8% ee, *S*) has been dramatically amplified to lead to alkanol **2**, with a significantly higher ee (94% ee, *S*). Globally, during these four consecutive autocatalyses (entries 1–4), the amount of the minor (*R*)-isomer has been multiplied by less than 500, whereas in the same time, the amount of the major (*S*)-enantiomer has been multiplied by a factor of more than 12,000.

From previous studies,[14] it is known that such asymmetric autocatalytic reactions imply dimeric zinc alkoxide species as active autocatalysts. As the size of the asymmetric amplification depends on the relative stabilities and the relative catalytic activities of homo- and heterochiral dimers, it may strongly depend on the experimental conditions in which the reaction is carried out. Several experimental parameters were, therefore, optimized in order to obtain the highest amplification of chirality (Table 3). Firstly, the autocatalytic reaction was carried out in the presence of 10 mol % of (*S*)-**2** with 88% ee at various concentrations in toluene (entries 1–5). Under highly dilute conditions, the asymmetric amplification is not significant (entry 1). However, a large amplification of chirality occurs at higher concentration. The highest asymmetric amplification was obtained when the initial concentration in alkanol **2** was of 3.4 mM. At this optimal concentration, starting from

Table 3. Optimization of the asymmetric amplification in toluene



Entry	Initial concentration in autocatalyst **2** (mM)	Initial molar ratio **2**:**1**:*i*-Pr_2Zn	Initial ee of autocatalyst **2** (%)	ee of the mixture of autocatalyst and product **2** after reaction (%)	Newly formed product **2**	
					Yield (%)	ee (%)
1	2.1	0.1:1:2.4	88 (*S*)	89 (*S*)	86	89 (*S*)
2	2.4	0.1:1:2.4	88 (*S*)	94 (*S*)	88	95 (*S*)
3	2.8	0.1:1:2.4	88 (*S*)	95 (*S*)	87	95 (*S*)
4	3.4	0.1:1:2.4	88 (*S*)	95 (*S*)	87	96 (*S*)
5	4.4	0.1:1:2.4	88 (*S*)	94 (*S*)	92	94 (*S*)
6	3.4	0.1:1:2.3	91 (*R*)	96 (*R*)	92	97 (*R*)
7	3.4	0.1:1:1.8	91 (*R*)	98 (*R*)	95	99 (*R*)
8	3.4	0.1:1:1.3	91 (*R*)	99 (*R*)	92	>99 (*R*)
9	3.4	0.1:1:1.1	91 (*R*)	98 (*R*)	83	99 (*R*)

an 88% ee (*S*)-autocatalyst **2**, the newly formed (*S*)-**2** reached 96% ee (entry 4). The influence of the molar ratio of dialkylzinc with regard to the aldehyde was then studied (entries 6–9). By decreasing the concentration in diisopropylzinc, the asymmetric amplification was also improved without a major loss in yield. Thus, when the reaction was catalyzed by 10 mol % of (*R*)-**2** with 91% ee in the presence of only 1.3 equiv of diisopropylzinc, the newly formed product was obtained with 92% yield as an analytically pure enantiomer [>99% ee, (*R*)-configuration].

Recently, considerable efforts were made to understand the mechanism of asymmetric autocatalysis better, particularly in the characterization of the structure of the autocatalyst.[14b,d–f] The present study shows that while a highly hindered alkynyl moiety at the 2-position of the autocatalyst does not prevent asymmetric amplification, it could provide significant information for determining which possible structures are more likely.

In addition, one of the great advantages of asymmetric autocatalysis consists in the possibility of performing several consecutive asymmetric amplifications in one pot.[15] Thus, rather than quenching the reaction and then isolating alkanol **2** after each asymmetric autocatalysis, it may be possible to obtain a high degree of chiral amplification in one flask by performing several periodical portionwise additions of pairs of diisopropylzinc and aldehyde **1**. By performing three periodic portionwise additions of pairs of diisopropylzinc and aldehyde **1**, (*S*)-alkanol **2** with only 2% ee has been automultiplied to finally give alkanol **2** with an enhanced 75% ee of the same absolute configuration.

3. Conclusion

Thus, chiral ferrocene-containing pyrimidyl alkanol **2** can be efficiently synthesized by asymmetric autocatalysis as an enantiomerically pure product. Moreover, during this autocatalytic reaction, a large amplification of the enantiomeric excess of the product occurs. In addition, a one-pot multi-step procedure has been developed and allowed us to obtain a high ee product from a nearly racemic autocatalyst.

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13. Typical experimental procedure is as follows (Table 1, entry 5): To a solution of (*S*)-1-(2-ferrocenylethynyl-5-pyrimidyl)-2-methylpropan-1-ol **2** (18 mg, 0.05 mmol, >99% ee) in cumene (12 mL) was slowly added diisopropylzinc (1.2 mL, 1 M solution in cumene, 1.2 mmol) at 0 °C under argon. After stirring the mixture for 30 min, solid 2-ferrocenylethynylpyrimidine-5-carboxaldehyde **1** (158 mg, 0.50 mmol) was slowly added via a powder funnel. After 3 h at 0 °C, the reaction was quenched with a mixture of aqueous ammonia and saturated aqueous ammonium chloride solution (7 mL) and extracted by methylene chloride. The combined organic layers were

dried over anhydrous sodium sulfate and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography (developing solvent: methylene chloride/ethyl acetate = 4:1) afforded 191 mg (97%) of (*S*)-1-(2-ferrocenylethynyl-5-pyrimidyl)-2-methylpropan-1-ol **2** with >99% ee (Chiralcel OD-H, hexane/ethanol = 80:20, 1 mL/min, *S*-isomer: 14.4 min; *R*-isomer: 32.5 min). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.60 (s, 2H), 4.61 (t, $J = 1.8$ Hz, 2H), 4.50 (d, $J = 5.6$ Hz, 1H), 4.30 (t, $J = 1.8$ Hz, 2H), 4.24 (s, 5H), 3.35 (s, 1H), 2.00–1.93 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.87 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.6, 152.0, 134.1, 89.2, 84.7, 75.0, 72.3, 70.1, 69.7, 62.1, 35.0, 18.4, 17.4. Mp = 141.5–142 °C (orange crystals). Elem. Anal. found: C, 66.64; H, 5.40; N, 7.87 (calcd: C, 66.68; H, 5.60; N, 7.78). HRMS (FAB+): found: 360.0921 (calcd: 360.0925). $[\alpha]_D^{18} = -18.0$ (*c* 0.99, $CHCl_3$) (>99% ee, *S* configuration). IR (KBr): cm^{-1} 3340, 2208, 1581, 1545, 1479, 1411.

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