Pergamon

Tetrahedron Letters 40 (1999) 831–834

TETRAHEDRON
LETTERS

Improved Stereoselectivity in the Heterogeneous Catalytic Synthesis of Enalapril Obtained Through Multidimensional Screening

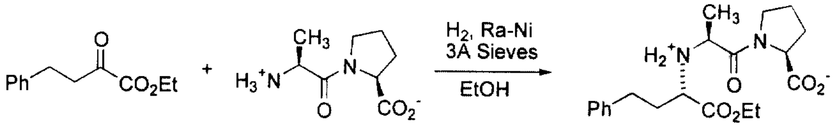
Mark A. Huffman* and Paul J. Reider

Department of Process Research
Merck Research Laboratories
P.O. Box 2000, Rahway, New Jersey 07065

Received 28 October 1998; revised 20 November 1998; accepted 23 November 1998

Abstract: A multidimensional screening of catalysts and additives led to the discovery of improved conditions for the diastereoselective reductive amination which produces enalapril. Additives acetic acid and potassium fluoride, which in isolation are detrimental, work together to improve the SSS : RSS selectivity with Ra-Ni in ethanol to 17 : 1 from 11 : 1. © 1999 Elsevier Science Ltd. All rights reserved.

The power of combinatorial chemistry in the discovery of molecules having desirable properties has inspired efforts to apply similar techniques to the discovery and optimization of chemical reactions.[1] The majority of reports on such endeavors concern homogeneous (or polymer-bound) catalyst discovery through the combinatorial synthesis of libraries of potential ligands followed by screening for catalytic properties.[2] In this paper, we report a somewhat different approach in which heterogeneous catalysts and potentially modifying additives are combined and evaluated in a multivariate fashion. The result is a unique set of reaction parameters which gives improved stereoselectivity and yield over the previous, highly optimized reaction conditions. It is highly improbable that these conditions would have been discovered by traditional methods.



2 **3** **1**

11 : 1 SSS/RSS

The large-scale synthesis of ACE inhibitor enalapril (**1**) involves a key diastereoselective reductive amination reaction between α-ketoester **2** and the dipeptide alanyl proline (**3**), catalyzed by Raney-Nickel.[3] The initially reported conditions gave a diastereomer ratio of 6.7 : 1. Over the past decade, this has been improved to 11 : 1 by traditional optimization, primarily of the Ra-Ni catalyst. The best ratio achieved with a catalyst other than Ra-Ni was 1.5 : 1 using palladium on carbon or IrO_2.

Because of the extensive study that has already gone into this reaction, we expected that it would be a challenging case to improve upon, and thus a good test case for a novel approach. The method used was a broad, rapid, two- and three-dimensional screening of heterogeneous catalysts with various additives, either singly or in combination with a second additive. Experiments were performed in a hydrogenation reactor in

PII: S0040-4039(98)02590-8

which up to 18 reactions in vials were stirred in a single vessel under one atm of hydrogen.[4] Reaction set-up was speeded by slurrying the common reagents for a set of reactions and distributing by pipetter. Yield and diastereomer ratio were determined by HPLC.[5]

After an initial catalyst screen, Ra-Ni, Pt/Al_2O_3, Pd/Al_2O_3, and Pd/C were selected for further experiments. Several hundred reactions were then run with these four catalysts and one or two additives, in most cases with the additives initially at 10 wt % vs. Ala-Pro. Additives were chosen from a number of classes, both chiral and achiral, including amino acid derivatives, carbohydrates, salts, organic acids, and Lewis acids.

One of the initial discoveries was that various cinchona alkaloids biased the reaction as much as 1 : 1.2 in favor of the undesired RSS isomer when combined with Pd/Al_2O_3 or Pd/C catalysts, compared with ratios of 1.6 : 1 and 1.4 : 1 in favor of SSS with these catalysts and no additives. Unlike the previously reported cinchona-modified Pt hydrogenation catalyst systems,[6] the effect here is apparently independent of absolute stereochemistry since, for example, quinine and quinidine gave nearly the same result.

Table 1. Effect of Salts and Acetic Acid on Pt/Al_2O_3 Reactions

acetic acid (25 %)	salt	equiv.	SSS : RSS	assay yield (SSS + RSS)
no	none		2.8 : 1	14
yes	none		4.6 : 1	58
yes	LiCl	4.8	6.4 : 1	50
yes	NaCl	1.8	4.9 : 1	62
yes	NaBr	2.8	6.4 : 1	68
yes	LiF	4.0	4.3 : 1	66
yes	KF	4.0	4.0 : 1	11

A more favorable discovery was that with Pt/Al_2O_3, a modest improvement in stereoselectivity occurred with several additives including some carbohydrates and some organic acids, such as pyroglutamic acid, citric acid, and acetic acid. The acetic acid charge was optimized to 25 % of the solvent by volume, giving a 4.6 : 1 SSS : RSS ratio vs. 2.8 : 1 in ethanol alone. Overall yield was also improved due to better chemoselectivity toward reductive amination vs. ketone reduction. Subsequently some salts were found to have a modest but reproducible effect on this Pt/Al_2O_3 reaction. Selected examples are shown in Table 1. The combination of NaBr and 25 % acetic acid in ethanol raised the Pt/Al_2O_3 catalyst performance from a 14 % yield and 2.8 : 1 stereoselectivity to 68 % yield and 6.4 : 1 ratio, a stereoselectivity approaching the 6.7 : 1 ratio initially reported for Ra-Ni.

A combined screen of salts with other additives and catalysts revealed another valuable combination: Ra-Ni, acetic acid, and KF. The initial hit at 25 % acetic acid in ethanol and 4 eq. KF gave a 17 : 1 ratio of SSS to RSS (Table 2). In optimizing this lead, the ratio of acetic acid to KF turned out to be important, but if varied together the quantity of both additives could be reduced while maintaining selectivity. The optimized conditions use 1.25 mol eq. acetic acid and 1.05 eq. KF (vs. Ala-Pro) at ambient temperature and one atm hydrogen.[7] The product is isolated as enalapril maleate by selective crystallization of the SSS diastereomer with maleic acid. The increased diastereoselectivity (17 : 1 vs. 11 : 1) leads to a significant isolated yield improvement in this high-volume, high-value drug.

Table 2. Effect of Fluorides and Acetic Acid on Raney-Nickel Reactions

acetic acid (25 %)	salt	equiv.	SSS : RSS	assay yield (SSS + RSS)
no	none		11 : 1	90
yes	none		11 : 1	89
no	KF	1.0	11 : 1	30
no	NaF	4.0	11 : 1	90
yes	CsF	1.0	14 : 1	89
yes	KF	4.0	17 : 1	90
yes	NaF	4.0	11 : 1	89

An important point about this discovery is that unlike the acetic acid/salt results for Pt/Al_2O_3, with Ra-Ni neither additive has a beneficial effect alone, and in fact KF without acetic acid inhibits the reaction. Also, the effect requires the specific, unique combination of Ra-Ni catalyst, acetic acid and KF. With the exception of substituting CsF for KF, a change in catalyst or either additive removes any benefit. For example, NaF has no effect on Ra-Ni reactions with or without acetic acid (Table 2), while adding KF to the combination of acetic acid and Pt/Al_2O_3 depresses yield and selectivity (Table 1). This leads to the conclusion that only experiments that simultaneously vary more than one factor would have discovered these reaction conditions. A more traditional method of optimizing one variable at a time would only find combinations in which each change alone provides a benefit.[8]

The result of this multidimensional screening effort was a process improvement which involves the addition of two inexpensive reagents and which significantly improves reaction selectivity and isolated yield. The value of simultaneously varying multiple parameters was demonstrated, and this approach may be fruitful when applied to any of the factors which can affect a reaction's outcome. The impact of this type of experimental plan would be multiplied by the use of additional automation in reaction set-up and assay.

Acknowledgement: We thank A.O. King for assistance in multiple hydrogenation reactor design, and Y. Sun and C. LeBlond for their work on optimization of the ultimate procedure.

REFERENCES AND NOTES

1. a) Sigman, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902. b) Cole, B.M.; Shimizu, K.D.; Krueger, C.A.; Harrity, J.P.A.; Snapper, M.L., Hoveyda, A.H. *Angew. Chem. Intl. Ed. Engl.* **1996**, *35*, 1668-1671. c) Burgess, K.; Lim, H.-J.; Porte, A.M., Sulikowski, G.A. *Angew. Chem. Intl. Ed. Engl.* **1996**, *35*, 220-222. d) Gilbertson, S.R.; Wang, X. *Tetrahedron Lett.* **1996**, *37*, 6475-6478. e) Liu, G.;

Ellman, J.A. *J. Org. Chem.* **1995**, *60*, 7712-7713. f) Menger, F.M.; Eliseev, A.V.; Migulin, V.A. *J. Org. Chem.* **1995**, *60*, 6666-6667. g) Gennari, C.; Nestler, H.P.; Piarulli, U.; Salom, B. *Liebigs Ann./Recueil* **1997**, 637-647.

2. For a novel approach to screening heterogeneous catalysts, see: Moates, F.C.; Somani, M.; Annamalai, J.; Richardson, J.T.; Luss, D.; Willson, R.C. *Ind. Eng. Chem. Res.* **1996**, *35*, 4801-4803.
3. Blacklock, T.J.; Shuman, R.F.; Butcher, J.W.; Shearin, W.E. Jr.; Budavari, J.; Grenda, V.J. *J. Org.Chem.* **1988**, *53*, 836-844.
4. The hydrogenation reactor consisted of a cylindrical glass vessel 9 cm in diameter, with a glass cap connected via an O-ring-sealed flange and clamp. A joint in the cap was connected to a hydrogen/nitrogen/vacuum manifold. Individual reaction mixtures were placed in 8 mL vials fitted with septum-containing screw caps. A short 18 gauge needle was placed through each cap to allow gasses to pass through while preventing cross-contamination by splashing. The vials were placed in a rack consisting of a circular teflon plate drilled with 18 wells to accommodate the vials. Magnetic stir bars in the vials allowed mixing with a strong magnetic stirrer placed under the reactor.
5. **Representative screening procedure**: Alanyl proline (1.395 g, 7.5 mmol) and powdered 3A sieves (2.88 g) were suspended in a mixture of absolute ethanol (11.25 mL) and acetic acid (3.75 mL). To the suspension was then added ethyl-2-oxo-4-phenylbutyrate (1.56 ml, 8.25 mmol). From the rapidly stirring suspension, 1.3 mL portions were removed by pipetter (with wide-bore tip) and transferred into 8 mL vials which had previously been charged with LiF (13 mg, 26 mg, 52 mg) or KF (29 mg, 58 mg, 116 mg). Some of the vials had also been previously charged with 10 mg of 5 % platinum on alumina; the remainder were charged with 100 mg of ethanol-wet Raney-Nickel after receiving the reagent slurry. The vials were placed in the glass pressure vessel (ref. 4). After vacuum/nitrogen purging, the mixtures were stirred under one atm hydrogen at ambient temperature for 21 h. Samples from each vial were diluted 1000X, filtered and assayed by HPLC using an autosampler.
6. Blaser, H.-U.; Jalett, H.-P.; Müller, M.; Studer, M. *Catal. Today* **1997**, *37*, 441-463.
7. **Optimized reaction conditions**: In a hydrogenation reactor, potassium fluoride (1.53 g, 26.3 mmol), alanyl proline (4.66 g, 25.0 mmol), powdered 3A sieves (9.6 g), and acetic acid (1.88 g, 31.3 mmol) are combined in 48 mL anhydrous ethanol. The mixture is inerted with nitrogen, and to it is added ethanol-wet Raney-Nickel (5.13 g). Ethyl-2-oxo-4-phenylbutyrate is added last (6.20 g, 27.5 mmol). After vacuum degassing, the mixture is stirred under one atm of hydrogen at 22 °C for 18 h. When reaction completion is confirmed by HPLC, the mixture is filtered through Solka Floc rinsing with ethanol. (Caution: Raney-Nickel must not be allowed to dry out.) Crystallization of the salt with maleic acid (ref. 3) gives 9.97 g, 81 %, vs. 76 % using the standard reaction conditions.
8. For a more extensive discussion of multidimensional reaction screening, see: Porte, A.M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180-9187.