CHEMICAL ENGINEERING TRANSACTIONS
VOL. 32, 2013
A publication of AIDIC
The Italian Association of Chemical Engineering
Online at: www.aidic.it/cet
Chief Editors: Sauro Pierucci, Jiří J. Klemeš

ISBN 978-88-95608-23-5; **ISSN** 1974-9791
DOI: 10.3303/CET1332325

Kinetic Chiral Resolution by Thin Layer Extraction

Ram Lavie*

Department of Chemical Engineering, Technion - Israel Institute of Technology, Haifa, 3200003 Israel

lavie@tx.technion.ac.il

A theoretical study of kinetic chiral resolution of ionic compounds by thin layer extraction, based on a model that has been successfully tested experimentally by others indicates that considerable resolution may be achieved in a single contacting stage provided the reaction rates of the two enantiomers are sufficiently differentiated. The role played by various design and operation parameters is delineated.

1. Introduction

Chiral resolution is a process for the separation of racemic compounds into their enantiomers. Enantiomers are obtained by asymmetric synthesis or by chiral resolution. Reactive liquid-liquid extraction promises to become an economic alternative chiral resolution method (Schuur et al., 2011). In liquid-liquid extraction, an aqueous solution of the racemate is equilibrated with an organic phase consisting of a solvent containing an organic chiral host. Some of each enantiomer transfers to the organic phase where it reacts reversibly with the host resulting in an unequal distribution of the enantiomers in the organic phase. The latter is then contacted with an aqueous strip solution, removing the enantiomers from the organic phase. Multistage operation amplifies the separation. Chiral resolution by extraction has so far been mostly been applied as an equilibrium process. Kinetic resolution that exploits a difference in the rates of reaction has been mentioned, with some reservations, in work dealing with asymmetric synthesis (Kagan,2001) but no significant breakthrough has been so far reported in the context of separation by extraction. Relative rates of reaction in the order of well above 10^2 have been reported (Vedejs and Jure, 2005). Lewis cells and centrifugal extractors that have been used for chiral resolution by extraction (Schuur et al., 2011) have non-negligible inventories of solutions and extractant, imposing mass transfer conditions that overshadow the reaction kinetics. Moreover, kinetic chiral resolution requires some flexibility in controlling the extent of reaction, a flexibility that is not availed in Lewis cells and centrifugal extractors or in any other conventional liquid-liquid extraction method. Thin Layer Extraction (TLX) (Lavie, 2008, 2011, 2011a), a time-periodic version of liquid-liquid extraction, reduces inventories to the minimum while also minimizing mass transfer resistance. Thus, instantaneous equilibrium between the phases is a reasonable approximation in TLX, making the kinetics stand out. Most importantly, it permits independent control of the time spent by uniform batches of each of the donor and strip aqueous phases while in intimate contact with the organic phase.
The present study explores the potential of TLX as a tool for kinetic resolution by extraction. Only isothermal, single stage, symmetric operation is discussed here.

2. Thin Layer Extraction

Thin Layer Extraction (TLX) is an intensive, time-periodic reactive liquid-liquid extraction method (Lavie, 2008, 2011) that implements a combined periodic extraction/back-extraction cycle. TLX uses an open, solid macro-porous matrix made of a microporous material to support a permanent thin layer of the organic phase. Two thin layers of solutions, one a donor and the other a strip, alternate at contacting the permanent thin layer of extractant in a frequent periodic cycle. The species of interest in the donor solution react with the host in the extractant to form a complexes that decompose later in the cycle to release the enantiomers into the strip solution at conditions that favor such release. In traditional continuous liquid-liquid extraction, extraction and stripping occur simultaneously at separate locations. In TLX (figure 1) extraction and back extraction take place at a same location but different times.

Please cite this article as: Lavie R., 2013, Kinetic chiral resolution by thin layer extraction, Chemical Engineering Transactions, 32, 1945-1950 DOI: 10.3303/CET1332325

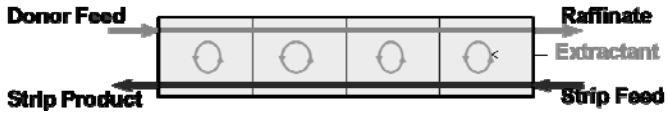


Figure 1 – The Multistage Thin Layer Extraction Structure

Three inherent characteristics of TLX make of it a particularly attractive method to implement kinetic resolution:

(a) Mass transfer resistance is negligible: with a molecular diffusivity in the order of 10^{-9} m^2/s, the characteristic time for diffusion through a 20μ thick layer is of the order of 0.4 s permitting frequent cycling between the donor and the strip liquids and distancing of the time scale of mass transfer from that of the reactions, all or some of which are taken to be slower.

(b) The inventory of the liquids participating in the process (both organic and aqueous) is minimal thereby favoring detailed control of the conditions prevailing in uniformly spread small batches of the processed fluids and allowing early "harvesting" along the reaction trajectory of the products, where differentiation between the enantiomers is most pronounced.

(c) Extraction and Strip action are distinctly separated in time, allowing individual tuning of their reaction time spans.

TLX kinetic resolution is implemented in a version of the Thin Layer Extraction equipment where batches of the aqueous donor and strip solutions are alternately sprayed onto the organic layer, left to wait and react briefly over specified time spans and are then collected as a raffinate product at one end and a strip product at the other.

The process cycles through a series of four consecutive steps:

(a) A batch F_e of aqueous feed at composition $[A_{ie}]_{aqf}$ and pH_e equilibrates with the organic layer whereby some neutral enantiomers transfer from the aqueous donor phase to the organic phase.

(b) While equilibrated with the aqueous batch, the enantiomers in the organic phase react with the host to form complexes at a forward rate k_{1i} and a backward rate k_{2i} for a time t_e at the end of which the aqueous batch is collected at composition $[A_{ie}(t_e)]_{aq}$ as a raffinate.

(c) A batch F_w of aqueous strip feed at composition $[A_{iw}]_{aqf}$ and pH_w equilibrates with the organic layer whereby some enantiomers transfer from the organic phase to the aqueous strip phase.

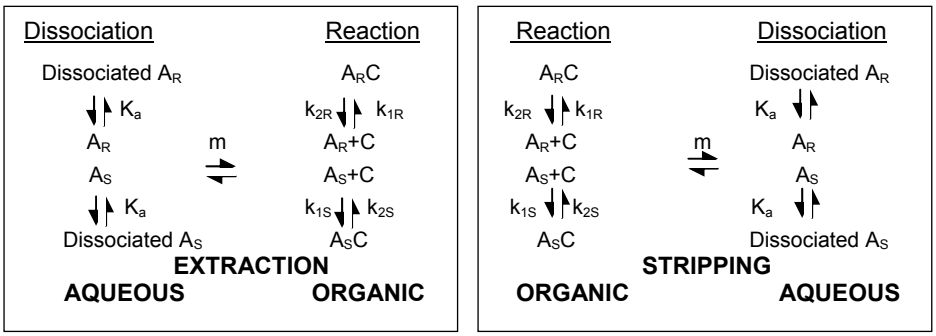
(d) While equilibrated with the aqueous strip batch, the enantiomers in the organic phase react with the host at forward and backward rates k_{1i} and k_{2i} for a time t_w at the end of which the aqueous batch is collected at composition $[A_{iw}(t_e+t_w)]_{aq}$ as a strip product.

The volumes of the aqueous feed batches F_e and F_w, relative to the volume E of the organic phase, determine the organic to aqueous (O/W) ratio in the respective steps. The separation effect obtained in one contacting cell may be multiplied through a multistage process where n cells are connected in series with the aqueous donor and strip streams flowing in countercurrent directions as depicted in figure 1.

The following analysis concerns a single isothermal TLX cell.

3. The mathematical model

The model in Scheme 1 is equivalent to the model used and tested by (Steensma et al., 2005, 2007) as well as by Schuur et al., 2010, 2011) and others. It has been adapted to the periodic kinetic conditions prevailing in kinetic TLX with a constantly prevailing equilibrium between the aqueous and organic phases.



Scheme 1 – The periodic kinetic model.

The enantiomers dissociate in the aqueous phases with only the neutral form distributing between the aqueous and the organic phases according to a distribution coefficient m. The enantiomers A_R, A_S, react with the host C in the organic phase at unequal rates k_{1R}, k_{2R}, k_{1S}, k_{2S}, to form complexes A_RC and A_SC. The host is never depleted.

The rates are related to the reaction equilibrium constants by: $K_{cR} = \frac{k_{1R}}{k_{2R}}, \quad K_{cS} = \frac{k_{1S}}{k_{2S}}$. (1)

The kinetic selectivity is defined by a pair of parameters:

$$\alpha_{\kappa 1} = Max\left\{\frac{k_{1R}}{k_{1S}}, \frac{k_{1S}}{k_{1R}}\right\} \quad \text{and} \quad \alpha_{\kappa 2} = Max\left\{\frac{k_{2R}}{k_{2S}}, \frac{k_{2S}}{k_{2R}}\right\} \tag{2}$$

The extraction and the stripping aqueous feeds are maintained at different pH, to drive enantiomers from the extraction feed to the organic phase to the strip product.

A mass balance on the organic phase leads to the mathematical model, with i = R, S, e=extraction, w=stripping:

$$(1+\frac{1}{D_e})\frac{d[A_{i\,e}]}{dt} = -k_{1i}[A_{i\,e}][C] + k_{2i}[A_iC], \quad [A_{i\,e}](0) = \frac{D_e}{1+D_e}\left\{\frac{m}{D_e}[A_{ie}]_{aqf} + [A_{iw}](t_e + t_w)\right\}$$

$$\frac{d[C]}{dt} = \frac{d[A_{Re}]}{dt} + \frac{d[A_{Se}]}{dt}, \qquad [C(0)] = [C](t_e + t_w)$$

$$\frac{d[A_iC]}{dt} = k_{1i}[A_{i\,e}][C] - k_{2i}[A_iC], \qquad [A_iC(0)] = [A_iC](t_e + t_w)$$

$$(1+\frac{1}{D_w})\frac{d[A_{iw}]}{dt} = -k_{1i}[A_{iw}][C] + k_{2i}[A_iC], \quad [A_{is}(0)] = \frac{D_w}{1+D_w}\left\{\frac{m}{D_w}[A_{iw}]_{aqf} + [A_{ie}](t_e)\right\} \tag{3}$$

$$\frac{d[C]}{dt} = \frac{d[A_{Rw}]}{dt} + \frac{d[A_{Sw}]}{dt}, \qquad [C(0)] = [C](t_e)$$

$$\frac{d[A_iC]}{dt} = k_{1i}[A_{iw}][C] - k_{2i}[A_iC], \qquad [A_iC(0)] = [A_iC](t_e).$$

All variables refer to the organic phase except where specifically subscripted by aq.

D_e and D_s are the extraction and stripping factors $D_e = \frac{Em}{F_e}, \quad D_w = \frac{Em}{F_w}$. (4)

The phase distribution is $m = \frac{[A_{i\,e}](t)}{[A_{ie}]_{aq}(t)} = \frac{[A_{iw}](t)}{[A_{iw}]_{aq}(t)}$. (5)

The neutral enantiomers in the aqueous feeds are $[A_{ie}]_{aqf} = \frac{[A_{i\,e}]_{aqf,all\ forms}}{(1+10^{(pH_e - pK_a)})}, \quad [A_{iw}]_{aqf} = \frac{[A_{iw}]_{aqf,all\ forms}}{(1+10^{(pH_w - pK_a)})}$. (6)

The performance is expressed in terms of the enantiomer excess ee and the yield η:

$$ee_{ie} = Max\left\{\frac{[A_{\mathrm{Re}}]_{aq}(t_e) - [A_{Se}]_{aq}(t_e)}{[A_{\mathrm{Re}}]_{aq}(t_e) + [A_{Se}]_{aq}(t_e)}, \frac{[A_{Se}]_{aq}(t_e) - [A_{\mathrm{Re}}]_{aq}(t_e)}{[A_{\mathrm{Re}}]_{aq}(t_e) + [A_{Se}]_{aq}(t_e)}\right\}$$

$$ee_{iw} = Max\left\{\frac{[A_{Rw}]_{aq}(t_e + t_w) - [A_{Sw}]_{aq}(t_e + t_w)}{[A_{Rw}]_{aq}(t_e + t_w) + [A_{Sw}]_{aq}(t_e + t_w)}, \frac{[A_{Sw}]_{aq}(t_e + t_w) - [A_{Rw}]_{aq}(t_e + t_w)}{[A_{Rw}]_{aq}(t_e + t_w) + [A_{Sw}]_{aq}(t_e + t_w)}\right\} \tag{7}$$

$$\eta_{ie} = \frac{[A_{ie}]_{aq}(t_e)}{[A_{ie}]_{aqf,all\ forms}}, \quad \eta_{iw} = \frac{[A_{iw}]_{aq}(t_e + t_w)}{[A_{ie}]_{aqf,all\ forms}} \tag{8}$$

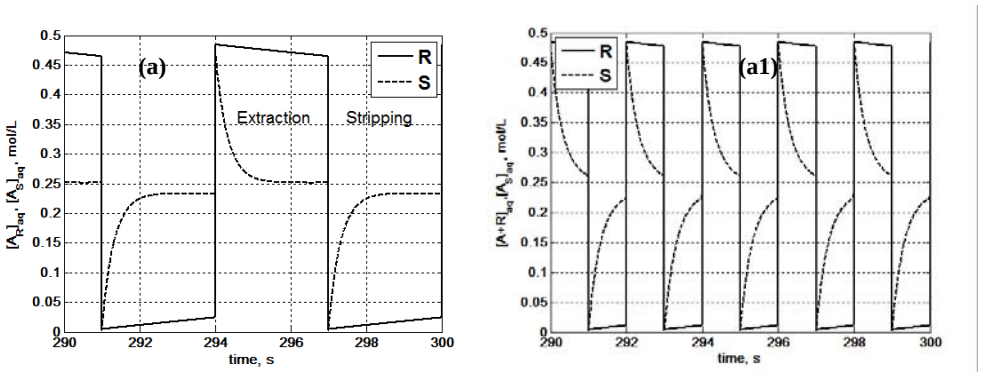


Figure 2 (a) - Raffinate and Strip product composition, mol/L . (a) $t_e = t_w$ = 3s, (a1) $t_e = t_w$ = 1s.

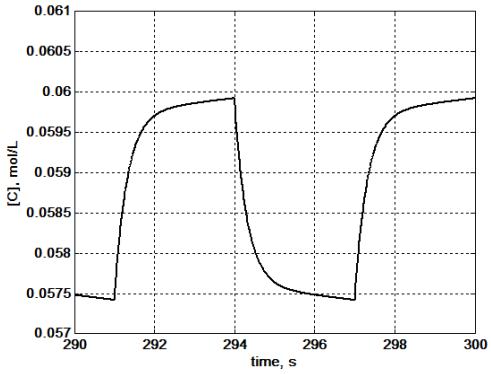


Figure 2(b) – Host concentration, mol/L

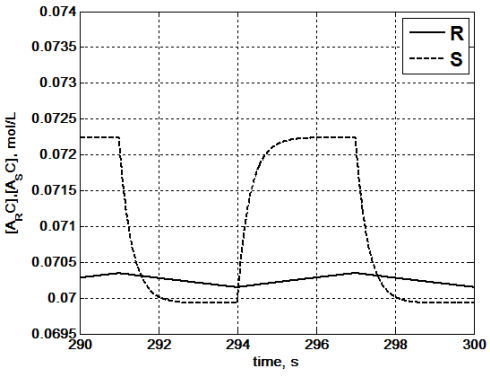


Figure 2(c) – Concentration of the complexes, mol/L

4. Mechanism of the kinetic TLX separation

The model (3) to (6) indicates that the separation occurs within the organic phase. Both the concentrations of the free enantiomers in the organic phase lessen in time during the extraction step and increase in time during the stripping step at different rates. One enantiomer lags behind the other in extraction and leads in front of the other in stripping. A gap between the concentrations develops depending on the kinetic selectivity $\{\alpha_{k1}, \alpha_{k2}\}$.

Typical plots in time of the concentrations of the enantiomers in the aqueous phase $[A_i]_{aq}$ (that are a direct reflection of their concentration in the organic phase), of the the host [C] and of the the complexes $[A_iC]$ are depicted in figure 2(a), (b) and (c) calculated for an arbitrary example with data: $t_e = t_w = 3$ s, k_{1R}=50 (L/mol)/s, k_{1S}=5,000 (L/mol)/s, $k_{2R} = 0.1 s^{-1}$, $k_{2S} = 10\ s^{-1}$, $F_e = F_w$=1 L, m=0.01 $(mol/L)_{org}/(mol/L)_{aq}$, pK_a =8.5, pH_e=7, pH_w=10, [C](0)= 0.06 mol/L, $[AR]_{aqef} = [AS]_{aqef}$ =0.5 mol/L, $[AR]_{aqwf} = [AS]_{aqwf}$ =0.

Comparing figures 2(a) and 2(a1), one may observe how, at equal conditions, the time span may lead to different product compositions in the two enantiomers. The performance obtained for this example is calculated, following equations (7) and (8) and tabulated in table 1.

Table 1 – Kinetic Resolution performance for the example depicted in figure 2.

t_e, s	t_w, s	ee_{Re}	ee_{Sw}	η_{Re}	η_{Sw}
3	3	0.2976	0.8127	0.9294	0.4669
1	1	0.2922	0.9030	0.9556	0.4469

Note that the rates in the above example are consistent with equal equilibrium constants for both enantiomers ($K_{cR} = K_{cS}$ = 500) or an equilibrium intrinsic selectivity $\alpha_{int}=K_{cR}/K_{cS}$=1. This does not stand in the way of obtaining kinetic resolution. Indeed, it can be observed in figures 3(a) and 3(c) that at high reaction rates that would be equivalent to long time spans $t_e \rightarrow \infty$ and $t_w \rightarrow \infty$ one obtains no separation at all.

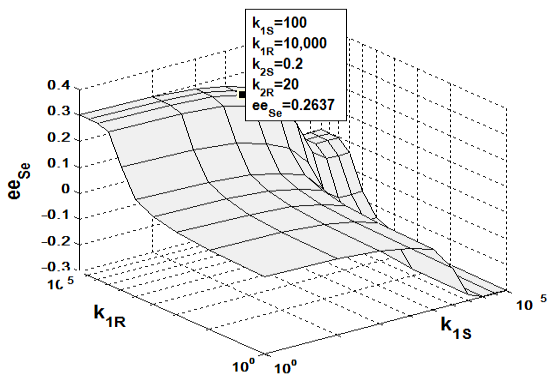


Figure 3(a) – Purity of Raffinate

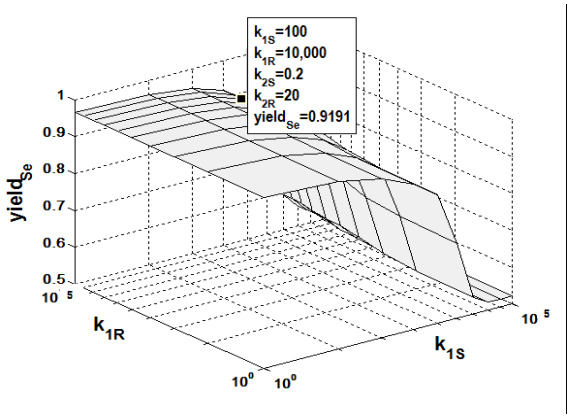


Figure 3(b) – Yield for Raffinate

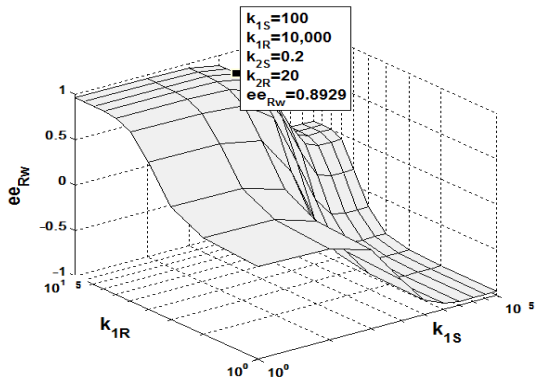


Figure 3(c) - Purity of Strip Product

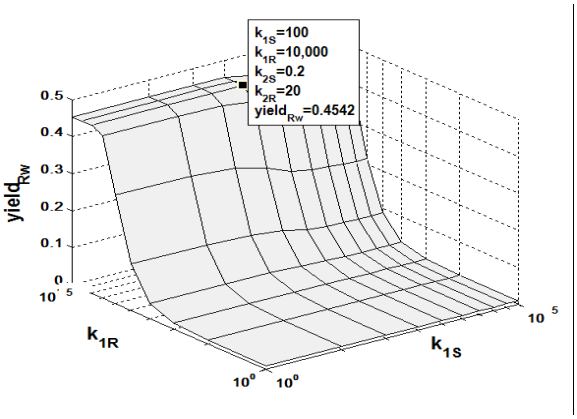


Figure 3(d) – Yield of Strip Product

5. Discussion of the design and operational parameters

The process outcome is dictated by design parameters including the choice of the host and the solvent that define for a given operating temperature:

(a) Four rates of reaction k_{ij} and

(b) The phase distribution coefficient m that is common to both enantiomers and both steps.

The outcome will also depend on operational parameters that include:

(a) The volumes F_e and F_w of the aqueous donor and strip feed batches that define the organic to aqueous ratios $(O/W)_j$,

(b) The pH_j of the two aqueous feeds and

(c) The time spans t_e and t_w of the extraction and strip steps.

5.1 Rates of reaction

The kinetic selectivity is determined, following equation (2), by the four reaction rates k_{1i}, k_{2i} of reaction (or following equations (1) and (2), by two equilibrium constants plus two reaction rates).

Figures 3 (a), (b), (c) and (d) map the purity and yield, as a function of the two forward reaction rates for the same example that was depicted above in figure 2.

Both the raffinate and the strip products exhibit a best combination of purity and yield when $k_{1R}/k_{1S} \geq 100$ and $k_{2R}/k_{2S} \geq 100$, conditions that have been reported in literature (Vedejs and Jure, 2005) to exist. Note again that kinetic resolution is obtained in this example even though the equilibrium intrinsic selectivity is $\alpha_{int} = 1$.

5.2 Enantiomer distribution m between the phases

The distribution m of the enantiomers between the organic and aqueous phases is a property of the participating materials (enantiomer, host and solvent). A small m reduces the average concentration of the enantiomers in the organic phase, helping purity to the detriment of throughput. Too large an m opens a free path from feed to strip product dwarfing the kinetic resolution mechanism. The value of m represents then an important consideration when choosing a solvent.

5.3 pH

The pH determines the fraction of the enantiomers in the aqueous feeds that are available in neutral form for participation in the process. However the logarithmic expression in equation 5 indicates that, in comparison to m, a relatively small gap with respect to the dissociation constant pK_a of the species goes a long way toward fulfilling the respective roles of the pH in the feed and product streams.

5.4 Time Spans of the transients

Table 1 indicates that, at least for the explored example and at a symmetric timing of extraction and striping, a short time span may be advantageous. There may be however a limit to this advantage because, as evident in figure 3, a high purity is mostly associated with a low yield over a wide range of reaction rate values. Also it may not be advisable to reduce the reaction time to the vicinity of the characteristic time of mass transfer.

5.5 Organic to aqueous ratio

The organic to aqueous ratios (E/F) influences the concentrations of the products through the extraction and stripping factors D_e and D_w in equations (3) and (4). A proportional dilution of both enantiomers in a

product should not affect its purity but would reduce yield .This may create an incentive to operate at a small organic to aqueous ratio in extraction that would incidentally also increase the raffinate throughput.

5.6 Host concentration

At the limit cycle, the free and the bound host concentrations cycle around some average values (see figures 2(b) and (c)) that depend on the initial host concentration. Up to a limit, a higher initial host concentration improves performance. In any case, the host concentration may be limited by its solubility and should be commensurate with the donor feed concentrate to ensure that the host is never depleted.

6. Conclusion

Kinetic Chiral Resolution by thin layer extraction is theoretically feasible. The required reaction rate ratios are large but within range of ratios that have been reported in literature. The equilibrium selectivity is irrelevant, permitting the consideration of host/solvent combinations that would have been rejected in the context of equilibrium extraction. Kinetic resolution relies on the availability of rate data that is less widespread than equilibrium data. However, when rate data is available, the model can help evaluate if and under what operating conditions TLX will provide a satisfactory resolution. The characteristics that are unique to TLX indicate that the computed results obtained for TLX should constitute an upper bound for the expected performance when applying kinetic resolution through other liquid-liquid extraction methods. Recent published data (Huang et al., 2013), appear to reinforce the assertion concerning the feasibility of kinetic resolution by extraction while also manifesting the limitations that inhibit performance when using conventional liquid-liquid extraction methods.

7. References

Huang, H., Nandhakumar,R., Choi,M., Su, Z. and Mook K. K. 2013 Enantioselective Liquid−Liquid Extractions of Underivatized General Amino Acids with a Chiral Ketone Extractant. J. Am. Chem. Soc. 135, 2653−2658 DOI:10.1021/ja3105945.

Kagan, H.B. 2001. Various aspects of the reaction of a chiral catalyst or reagent with a racemic or enantiopure substrate. Tetrahedron 57, 13, 2449-2468.

Lavie R. 2008 Thin Layer Extraction - a novel Liquid-Liquid Extraction Method. AIChE Journal. 54, 4, 957-964, DOI: 10.1002/aic.11445.

Lavie R. 2011 Method and Apparatus for Liquid-liquid Extraction. US Patent 8,021,554, Sept. 20, 2011.

Lavie R. 2011a. Chiral resolution of ionic compounds by thin layer extraction. Ind. & Eng. Chem. Res. 50, 22, 12311-12844, DOI: 10.1021/ie201596n.

Schuur B., Verkuijl B.J.V., Minnaard A.J. , de Vries J.G., Heeres H.J. and Feringa B.L. 2011. Chiral separation by enantioselective liquid–liquid extraction. Organic & Biomolecular Chemistry, 9, 1, 36-51. DOI: 10.1039/c0ob00610f.

Schuur B.; Winkelman J. G. M.; deVries J. G.; Heeres H. J. 2010. Experimental and Modelling Studies on the Enantio-separation of 3,5-dinitrobenzoyl-(R),(S)-leucine by Continuous Liquid–liquid Extraction in a Cascade of Centrifugal Contactor Separators. Chem. Eng. Sci. 65, 4682-4690. DOI:10.1016/j.ces.2010.05.015.

Steensma M.; Kuipers N. J. M. ; de Haan A. B.; Kwant G. 2007. Modelling and Experimental Evaluation of Reaction Kinetics in Reactive Extraction for Chiral Separation of Amines, Amino acids and Amino-alcohols. Chem. Eng. Sci., 62, 1395-1407. DOI:10.1016/j.ces.2006.11.043.

Steensma, M. 2005. Chiral separation of amino-alcohols and amines by fractional reactive extraction Thesis, University of Twente, The Netherlands ISBN: 90-9019313-8.

Vedejs E. and Jure M. 2005. Efficiency in Nonenzymatic Kinetic Resolution. Angew. Chem. Int. Ed. 44, 3974–4001. DOI: 10.1002/anie.200460842.