Faster and cleaner dynamic kinetic resolution via mechanochemistry

Thomas-Xavier Métro, Xavier Salom-Roig, Maëva Reverte, Jean Martinez, Frédéric Lamaty

To cite this version:


HAL Id: hal-02336877
https://hal.archives-ouvertes.fr/hal-02336877
Submitted on 29 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Faster and cleaner dynamic kinetic resolution via mechanochemistry

Thomas-Xavier Métro,* Xavier J. Salom-Roig, Maëva Reverte, Jean Martinez and Frédéric Lamaty*

Application of the ball-milling techniques to dynamic kinetic resolution accelerates reactions while avoiding the use of toxic organic solvents and reactants commonly required in these processes. In this way, dynamic kinetic resolutions can be both faster and “cleaner” in the sense that mechanochemistry enables the reduction of their environmental impact.

Controlling the optical purity of molecules is essential in many areas, particularly in pharmaceutical research where biological activity highly depends on the chirality of active compounds. Numerous highly stereoselective methodologies have been developed to access enantiopure molecules and among them, kinetic resolution provides an attractive approach. In this process, two enantiomers of a racemate are transformed into chiral products at different rates. When the resolution is efficient, one of the enantiomers of the racemic mixture is transformed into the desired product while the other is recovered unchanged.

However, this procedure is limited to a maximum theoretical yield of 50%. To overcome this limitation, an in situ epimerization of the chirally labile substrate can be combined with the kinetic resolution to become a dynamic kinetic resolution (DKR).3 However, the inherent necessity for the speed of product formation to be slower than the substrate epimerization usually makes dynamic kinetic resolution quite a slow process.

a-Halo carboxyls (A, Scheme 1) can be taken as a good illustration of this process: the configurationally labile halogen atom in the α position of the carbonyl can be irreversibly substituted by a nucleophile. Stereo-differentiation in the Sn2 halogen displacement can be controlled by the chiral environment on R2.

Scheme 1 Dynamic kinetic resolution of α-halo carboxyls by Sn2 halogen displacement.

Whereas DKR of such substrates allow access to products of type B with good yield and diastereoselectivity, long reaction times are needed. As many other examples of Sn2 reactions, these DKR require polar and aprotic solvents such as toxic DCM or THF,2 and are performed with organic, toxic and corrosive bases such as Et3N to epimerise the substrate.3 Thus, reaction conditions allowing shorter reaction times and avoiding the use of problematic solvents and reagents would be highly preferable. Following our general objective to find greener alternatives to otherwise environmentally troublesome chemical reactions,4 we envisioned performing DKR avoiding the use of undesirable solvents and bases. Due to its relevance for a laboratory scale study, the Ecoscale score5 was chosen as the green metric of choice to evaluate the environmental impact of the new reaction conditions. The Ecoscale is a score ranging from 0 (totally failed reaction) to 100 (ideal reaction) that is based on yield, cost, safety, technical set up, temperature and time of reaction, work up and purification aspects. To each of these parameters are attributed penalty points that are subtracted to the ideal score of 100 to give the Ecoscale score of the studied reaction. The reaction conditions are ranked excellent if Ecoscale score is > 75, acceptable if > 50 and inadequate if < 50.

As a first example, we studied the DKR reaction of α-bromo-(R)-pantolactone ester 1 with Br2NH that was previously described by Durst and coworkers.6 Thus, we treated compound 1 with Et3N, a catalytic amount of TBAI and Br2NH to obtain the corresponding α-dibenzylylamino ester 2a in 59% yield with an excellent diastereoisomeric ratio (>98:2) (Table 1, entry 1). As described in the literature, this reaction was set up using an excess of Et3N (2.0 eq) in a toxic solvent (THF is suspected to be carcinogenic), accounting for a low Ecoscale score of 42.5, which corresponds to an inadequate synthesis.5 To improve the environmental impact of this reaction, we envisioned replacing the problematic Et3N and THF with innocuous NaHCO3 and water.7 Under these conditions, the Ecoscale score was hardly improved to 54, mainly due to a low yield of 34% (50% brsm; Table 1, entry 2). In addition, the reaction was much slower as 6 h were necessary to reach 50% conversion and 2a was obtained with a lower diastereomeric ratio (87:13). When a preferable solvent such as EtOAc8 was used in place of water, the reaction proceeded with a satisfying Ecoscale score of 62.5, and furnished 2a in a good yield of 73% with an excellent diastereomeric ratio (>98:2) (Table 1, entry 3). Even when careful attention was paid to use the minimum amount of solvent enabling proper agitation of this heterogeneous reaction media, 6 days were necessary to reach full conversion of the substrate. At this point of the study, we considered that keeping innocuous NaHCO3 as base would force us to use more polar solvents such as EtOH, THF or DMF. The use of THF or EtOH as solvents was disappointing since 24 h and more than 6 days of reaction were respectively required to reach 95% of conversion (Table 1, entries 4 and 5). The use of DMF as solvent resulted in a much shorter reaction time; only 2 h were required for a complete consumption of substrate 1 (Table 1, entry 6). Nevertheless, an unsatisfying Ecoscale score of 50.5 was obtained mainly due to the low yield (55%) and the fact that DMF presents high health-related risks, which hamper its environmental impact.9 Excepted for DMF, these relatively long reaction times could be attributed to the low solubility of either NaHCO3 in organic solvents or α-bromo ester 1 in water, resulting in heterogeneous reaction mixtures that may lead to mass transfer limitations. As heterogeneity of the reaction mixture could be responsible for a low speed of reaction, the transformation was performed using the ball-milling technology.10 In this kind of apparatus, reagents (liquid or solid) are introduced into a jar with one or more balls. Rapid movements of the jar create repeated and violent contacts between reagents, balls and walls allowing for a very efficient mixing of solid-containing reaction mixtures.

* Institute of Chemistry of Polymers (InCPol), University of Montpellier, Place E. Bataille, 34095 Montpellier, France.

1 Presented at the 120th National Meeting of the American Chemical Society, March 21-26, 2010, Philadelphia, PA.


Table 1 Influence of the solvent, base, and homogenization technique on the DKR of 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Homogenization technique</th>
<th>Base (eq)</th>
<th>Solvent</th>
<th>Time to reach &gt;95% conversion</th>
<th>Yield (%)</th>
<th>dr (2a):(2b)</th>
<th>Ecoscale score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Magnetic stirring</td>
<td>Et₃N (2.0)</td>
<td>THF</td>
<td>5 h</td>
<td>59</td>
<td>&gt;98:2</td>
<td>42.5</td>
</tr>
<tr>
<td>2</td>
<td>Magnetic stirring</td>
<td>NaHCO₃ (1.2)</td>
<td>Water 6</td>
<td>6 h</td>
<td>34 (50)</td>
<td>&gt;98:2</td>
<td>87:13</td>
</tr>
<tr>
<td>3</td>
<td>Magnetic stirring</td>
<td>NaHCO₃ (1.2)</td>
<td>EtOAc 6</td>
<td>days</td>
<td>73</td>
<td>&gt;98:2</td>
<td>62.5</td>
</tr>
<tr>
<td>4</td>
<td>Magnetic stirring</td>
<td>NaHCO₃ (1.2)</td>
<td>THF</td>
<td>24 h</td>
<td>62</td>
<td>&gt;98:2</td>
<td>62.5</td>
</tr>
<tr>
<td>5</td>
<td>Magnetic stirring</td>
<td>NaHCO₃ (1.2)</td>
<td>EtOH</td>
<td>&gt;6 days</td>
<td>63</td>
<td>&gt;98:2</td>
<td>62.5</td>
</tr>
<tr>
<td>6</td>
<td>Magnetic stirring</td>
<td>NaHCO₃ (1.2)</td>
<td>DMF</td>
<td>2 h</td>
<td>55</td>
<td>&gt;98:2</td>
<td>50.5</td>
</tr>
<tr>
<td>7</td>
<td>Ball-milling</td>
<td>NaHCO₃ (1.2)</td>
<td>Solvent-free</td>
<td>30 min</td>
<td>62</td>
<td>&gt;98:2</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>Ball-milling</td>
<td>NaHCO₃ (1.2)</td>
<td>Water (η = 2)</td>
<td>15 min</td>
<td>96</td>
<td>&gt;98:2</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>Ball-milling</td>
<td>NaHCO₃ (1.2)</td>
<td>Water (η = 1)</td>
<td>15 min</td>
<td>94</td>
<td>&gt;98:2</td>
<td>79</td>
</tr>
</tbody>
</table>

* Determined by HPLC. † Isolated yield. ‡ Determined using 300MHz ¹H NMR. § Time to reach 50% conversion. ¶ Obtained as a 50:50 molar mixture of 2a:2b. * Based on recovered starting material (brsm). ‖ Not determined. ' The η ratio is defined as the amount of added liquid to the sum of the mass of reactants. It is expressed in µL mg⁻¹.

Indeed, 30 min of vigorous agitation were enough for a complete conversion of α-bromo ester 1 into amino-ester 2a when 1 was placed in a 10 mL jar with one 10 mm diameter ball, NaHCO₃, dibenzylamine, and TBAI in the absence of any solvent (Table 1, entry 7). Under these conditions, dibenzylamino ester 2a was isolated in 62% yield with an excellent diastereomeric ratio (>98:2) and a satisfying Ecoscale score of 63. Obtainable benefits from adding a liquid in a grinded reaction mixture are now well established. Indeed, when adding small amounts of water in the jar (η ratio of 2 µL mg⁻¹) only 15 min were necessary to obtained complete conversion of the substrate while dibenzylamino ester 2a was isolated in excellent yield and diastereomeric ratio (96% yield, dr > 98:2; Table 1, entry 8). In these conditions, the highest Ecoscale score was obtained (80), corresponding to an excellent synthesis. Calculations leading to this high Ecoscale score include solvent used during work-up and chromatographic purification (details on the Ecoscale calculations are available in the ESL). Reducing the amount of water in the reaction media to 1 µL mg⁻¹ had little effect on the course of the reaction as 2a was obtained in 94% yield and >98:2 dr (Table 1, entry 9). We postulate that solving the suspected mass transfer limitations by using the tremendous ability of the ball-mill technology to mix solid-containing mixtures allowed:

- improvement of the yield without hampering the diastereoselectivity
- reduction of reaction time
- utilisation of the least problematic base (NaHCO₃) and solvent (H₂O) regardless of their solubility or solubilising capacities.

To our knowledge, this is the first example of DKR to be performed through ball-milling technology.

At this stage of the study, we became interested in comparing the efficiency and the environmental impact of solution-based DKR reactions with the mechanochemistry-mediated approach on other known DKR reactions implying a Sn2 halogen substitution.

When treated with (S)-(−)-α-methylbenzylamine in THF in the presence of Et₃N as base, α-bromo ester 1 was transformed into 3 in 84% yield and >98:2 dr (Table 2, entry 1). The use of THF and Et₃N resulted in a low Ecoscale score of 52. Replacing these problematic chemicals with water and NaHCO₃ while mixing the reaction mixture with a vibrating ball-mill allowed for the production of 3 with much better Ecoscale score (72), high yield (80%) and diastereoselectivity (>98:2) (Table 2, entry 2). Treating α-bromo ester 1 with p-anisidine in classical solution-based approach furnised amine 4 in 75% yield and >98:2 dr, though with a low Ecoscale score of 40.5. When applying our ball-milled mediated approach, Ecoscale score could be improved up to 54, yet with a slightly lower yield (64%) and a drop in diastereoselectivity (88:12) (Table 2, entry 4). Oxygen-based nucleophiles such as p-methoxyphenol could also be used to perform DKR on α-bromo ester 1. Indeed, Durs and coworkers utilised NaH and THF to produce 5 with 70% yield and 95:5 dr, yet with a low Ecoscale score of 41 (Table 2, entry 5). Treatment of α-bromo ester 1 with p-methoxyphenol in a ball-mill with water and NaHCO₃ instead of THF and NaH resulted in the production of ester 5 with a better yield and Ecoscale score of 86% and 62 respectively, albeit with a moderate 72:28 dr (Table 2, entry 6). When 2,6-dichlorophenol was used as nucleophile, reaction time, diastereoselectivity and Ecoscale score were improved while the yield remain similar (Table 2, entries 7 and 8). After having changed the nature of nucleophiles, we focused our attention on other types of substrate such as α-bromo amide 7 and α-bromo ketone 9.

When 1-(2-bromo-1-oxopropyl)-L-proline methyl ester 7 was reacted with Bn₂NH in CH₂Cl₂ in the presence of Et₃N for 24 h, N,N-dibenzyld-D-alanyl-L-proline methyl ester 8 was obtained in 81% yield with 87:13 dr, accounting for an Ecoscale score of 51 (Table 2, entry 9). Once again, utilising the ball-milling technology avoided the use of problematic CH₂Cl₂ and Et₃N. Thus, the reaction of α-bromo amide 7 with Bn₂NH in the presence of NaHCO₃ and water in a vibrating ball-mill furnished product 8 with a similar yield (75%) and an improvement in the Ecoscale score was obtained (68.5 vs 51 with the solution-based approach) (Table 2, entry 10). It is worth noting that utilisation of the ball-mill also resulted in improving the diastereomeric ratio from 87:13 to >98:2.
Finally, this approach was applied to the DKR reaction of \( \gamma \)-bromo-\( \beta \)-ketosulfoxide 9 with \( \text{Bn}_{2}\text{NH} \). Salom-Roig and coworkers\(^\text{17}\) reported that treatment of 9 with 2.5 equivalents of \( \text{Bn}_{2}\text{NH} \) required 10 days in THF to reach reaction completion furnishing \( \gamma \)-dibenzylamino-\( \beta \)-ketosulfoxide 10 with 74% yield and \( >95:5 \text{ dr} \) (Table 2, entry 11). By using \( \text{Bn}_{2}\text{NH} \) as nucleophile and base to deprotonate the HBr salts produced during the course of the reaction, the authors already avoided the use of the flammable, corrosive and toxic \( \text{Et}_3\text{N} \), thus improving the environmental impact of the reaction. This particularity resulted in a good Ecoscale score of 58. Yet, when the same reaction was performed in a ball-mill with water replacing THF, time for reaction completion were dramatically reduced to only 7 h, while furnishing \( \gamma \)-dibenzylamino-\( \beta \)-ketosulfoxide 10 with a similar yield of 71% and diastereoselectivity (Table 2, entry 12). Replacing THF with water and reducing the required time to reach reaction completion resulted in an Ecoscale score improvement up to 66.5.

**Conclusions**

In conclusion, the great capacity of the ball-milling technology to mix solid-containing reaction mixtures allowed the design of reaction conditions that could mitigate the environmental impact of dynamic kinetic resolutions. This reduction was evaluated by calculating the Ecoscale score of every studied reaction conditions. Thus, we have shown that problematic chemicals such as THF or \( \text{Et}_3\text{N} \) could be replaced by innocuous water and \( \text{NaHCO}_3 \) without dramatically hampering the performance of the DKR reactions. In all cases, time required to go to completion was severely reduced and in some cases yields and/or

---

**Table 2** Comparison of classical solvent-based approaches with mechano-mediated DKR

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Homogenization technique</th>
<th>Base</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield (%(^a))</th>
<th>diastereoselectivity</th>
<th>Ecoscale score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>Magnetic stirring</td>
<td>( \text{Et}_3\text{N} )</td>
<td>THF</td>
<td>7 h</td>
<td>84</td>
<td>( &gt;98.2 )</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>Ball-milling</td>
<td>( \text{NaHCO}_3 )</td>
<td>Water</td>
<td>30 min</td>
<td>80</td>
<td>( &gt;98.2 )</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>Magnetic stirring(^b)</td>
<td>( \text{Et}_3\text{N} )</td>
<td>THF</td>
<td>7 h</td>
<td>75</td>
<td>( &gt;98.2 )</td>
<td>40.5</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>Ball-milling</td>
<td>( \text{NaHCO}_3 )</td>
<td>Water</td>
<td>6 h</td>
<td>64</td>
<td>88:12(^c)</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Substrate 5" /></td>
<td><img src="image10.png" alt="Product 5" /></td>
<td>Magnetic stirring(^d)</td>
<td>( \text{NaH} )</td>
<td>THF</td>
<td>6 h</td>
<td>70</td>
<td>95.5</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Substrate 6" /></td>
<td><img src="image12.png" alt="Product 6" /></td>
<td>Ball-milling</td>
<td>( \text{NaHCO}_3 )</td>
<td>Water</td>
<td>2 h</td>
<td>86</td>
<td>72:28(^d)</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Substrate 7" /></td>
<td><img src="image14.png" alt="Product 7" /></td>
<td>Magnetic stirring(^d)</td>
<td>( \text{NaH} )</td>
<td>THF</td>
<td>7 h</td>
<td>78</td>
<td>50:50</td>
<td>23.5</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15.png" alt="Substrate 8" /></td>
<td><img src="image16.png" alt="Product 8" /></td>
<td>Ball-milling</td>
<td>( \text{NaHCO}_3 )</td>
<td>Water</td>
<td>1 h 30</td>
<td>77</td>
<td>56:44(^d)</td>
<td>47.5</td>
</tr>
<tr>
<td>9</td>
<td><img src="image17.png" alt="Substrate 9" /></td>
<td><img src="image18.png" alt="Product 9" /></td>
<td>Magnetic stirring(^e)</td>
<td>( \text{Et}_3\text{N} )</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>24 h</td>
<td>81</td>
<td>87:13</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td><img src="image19.png" alt="Substrate 10" /></td>
<td><img src="image20.png" alt="Product 10" /></td>
<td>Ball-milling</td>
<td>( \text{NaHCO}_3 )</td>
<td>Water</td>
<td>13 h</td>
<td>75(^f)</td>
<td>( &gt;98.2 )</td>
<td>68.5</td>
</tr>
<tr>
<td>11</td>
<td><img src="image21.png" alt="Substrate 11" /></td>
<td><img src="image22.png" alt="Product 11" /></td>
<td>Magnetic stirring(^g)</td>
<td>( \text{Bn}_{2}\text{NH} )</td>
<td>THF</td>
<td>10 days</td>
<td>74</td>
<td>( &gt;95.5 )</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td><img src="image23.png" alt="Substrate 12" /></td>
<td><img src="image24.png" alt="Product 12" /></td>
<td>Ball-milling</td>
<td>( \text{Bn}_{2}\text{NH} )</td>
<td>Water</td>
<td>7 h</td>
<td>71</td>
<td>( &gt;98.2 )</td>
<td>66.5</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield. \(^b\) Not indicated in the original publication. \(^c\) Diastereomeric ratios were determined using 300MHz \(^1\)H NMR. \(^d\) 2.16 eq of \( \text{Bn}_{2}\text{NH} \) were used. \(^e\) 2.5 eq of \( \text{Bn}_{2}\text{NH} \) were used.

---
diastereomeric ratios were also improved. Exemplification of utilisation of the ball-milling technology to reduce the environmental impact of other problematic reactions is currently under progress.

We thank CNRS, Université Montpellier 1 and Université Montpellier 2 for financial support. François Métro is gratefully acknowledged for producing graphical abstract artwork.

Notes and references

Institut des Biomolécules Max Mousseron (IBMM), UMR 5247 CNRS-Universités Montpellier 1 et 2-ENSCM, Bâtiment Chimie (17), Université Montpellier 2, Place Eugène Bataillon, 34095 Montpellier cedex 5, France. Fax: (+33) 4-6714-4866; E-mail: tmetro@univ-montp2.fr

† Electronic Supplementary Information (ESI) available: General experimental procedures, characterisation data of all synthesized compounds and details on the calculations of Ecoscale scores.

2. DCM stands for dichloromethane and THF for tetrahydrofuran. DCM and THF are classified as toxic and carcinogenic (Category 2) according to Regulation (EC) No 1272/2008.
3. Triethylamine is classified as highly flammable (R11), corrosive (R35) and harmful (R20/21/22) according to EU Directives 67/548/EEC or 1999/45/EC.
7. NaHCO₃ is considered to be a not hazardous substance as defined by the European regulation N°1272/2008 and not classified as dangerous according to Directive 67/548/EEC.
9. DMF is classified as presenting reproductive toxicity according to Regulation (EC) No 1272/2008.
13. The η ratio is defined as the amount of added liquid to the sum of the mass of reactants. It is expressed in μL·mg⁻¹.