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Double Catalytic Kinetic Resolution (DoCKR) of Acyclic *anti*-1,3-Diols using Additive Horeau Amplification

Jérémy Merad,[a] Prashant Borkar,[a] Frédéric Caijo,[b] Jean-Marc Pons,[a] Jean-Luc Parrain,[a] Olivier Chuzel*[a] and Cyril Bressy*[a]

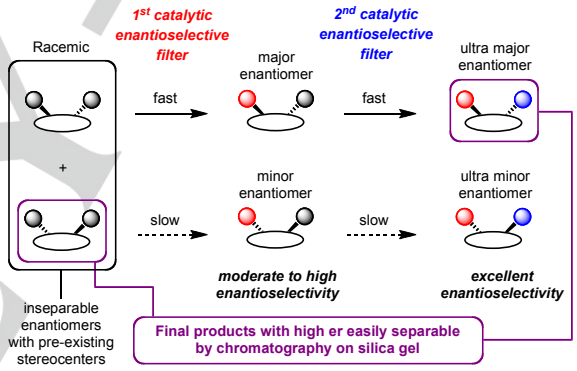
Abstract: The concept of synergistic double catalytic kinetic resolution (DoCKR) described in this article, was successfully applied to racemic acyclic *anti*-1,3-diols, a common motif in natural products. This process takes advantage of an additive Horeau amplification involving two successive enantioselective organocatalytic acylations reactions, and leading to diesters and recovered diols with high enantiopurities. It was first developed with C_2-symmetrical diols and then further extended to non-C_2-symmetrical *anti* diols to prepare useful chiral building blocks. The protocol is highly practical as it only requires 1 mol% of a commercially available organocatalyst and leads to easily separable products. This procedure was applied to the shortest reported total synthesis of (+)-cryptocaryalactone, a natural product with anti-germinative activity.

How can one improve the enantioselectivity outcome of a reaction on a wide scope? This is a recurring question during the development of any given catalytic enantioselective transformation. The indispensable optimization stage improves the enantiomeric ratio (er) of a reaction through the variations of the chemical and/or physical parameters of the transformation. Usually, er enhancement is rapidly accompanied by a narrowing of the reaction scope. Most of the time, the rational design of the catalyst structure is the only option to improve reactivity and selectivity. This fine tuning is nonetheless time consuming while it can result in negligible improvements due to the difficulty of considering all the parameters involved in the enantiodetermining transition state.

On the other hand, the Horeau principle[1] is responsible for the improvement of enantioselectivity in some reactions relying on polyfunctionalized substrates. By applying at least two identical successive enantioselective transformations, the second reaction can act as an additional sterecontrolling filter improving the enantiopurity of the final product. Since the pioneering works of Horeau in the 70's, such amplification of enantioselectivity was observed in several catalytic transformations.[2,3,5e] In enantioselective catalysis, the Horeau amplification can be divided into two main categories:

(1) In the *subtractive Horeau amplification*, the minor enantiomer obtained after the first transformation is the substrate of the second transformation. The polyfunctionalized substrates involved in this first category are either prochiral[3,4] or *meso* compounds.[3,5]

(2) In the *additive Horeau amplification*, the major enantiomer formed after the first reaction is rapidly consumed in the second enantioselective (or diastereoselective) transformation.[6] However, and oppositely to subtractive processes, examples of additive amplifications involving starting materials with pre-existing stereocenters are extremely scarce (Scheme 1).[7]



Scheme 1. Additive Horeau amplification applied to substrates bearing pre-existing stereocenters.

Although observed many times, the Horeau amplification is still considered as an anecdotal phenomenon. By considering the synthetic potential supported by the Horeau principle in enantioselective catalysis, we supposed that this concept could be used as a synthetic strategy by itself. Indeed, it could constitute an alternative approach to laborious catalyst fine-tuning while keeping high enantioselectivities and broad reaction scopes. In practice, the syntheses designed on this principle would require minimal optimization stage and remain effective with moderately selective catalysts. In order to validate this hypothesis we identified the double catalytic kinetic resolution (DoCKR) of acyclic *anti* 1,3-diols as a relevant transformation, complementary to our previous study.[5d] Indeed, this widespread stereodefined scaffold is, to a large extent, responsible for the biological activity of numerous polyketides such as dictyostatin, ripostatin B, fostriecin and peluroside A.[8] Consequently, the control of relative and absolute configurations is particularly pivotal.[9] Generally, these motifs are reached thanks to the preparation of an enantioenriched β-hydroxyketone followed by its *anti*-diastereoselective reduction[10] (Scheme 2a). However, few methods are catalytic and enantioselective.[6f,6g,11] In view, a

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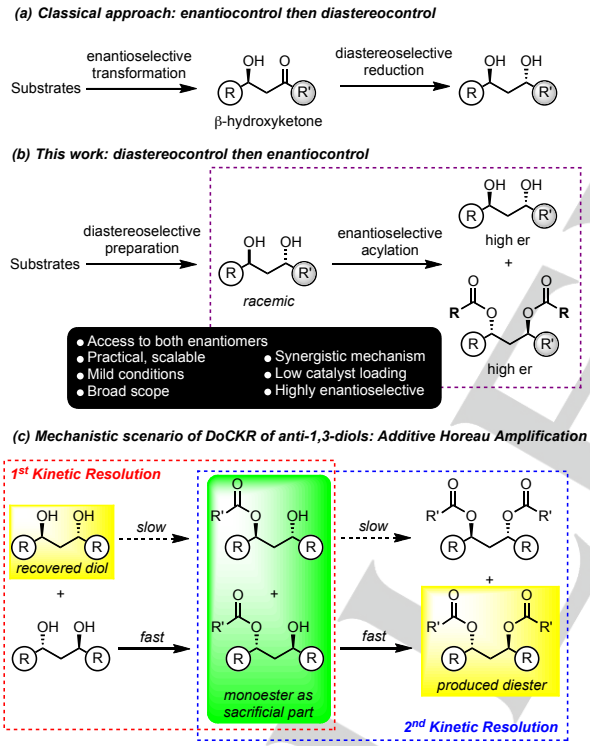
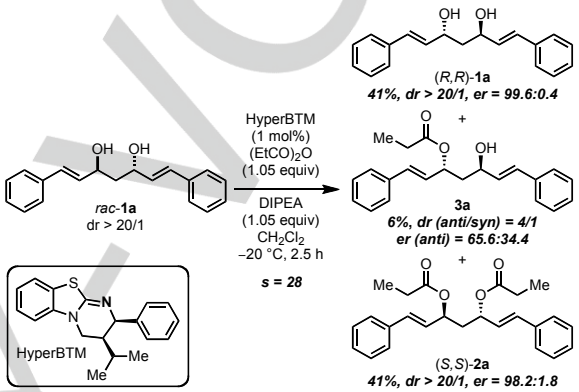
conceptually opposite approach setting first the diastereoselectivity and then securing the enantiocontrol could offer new opportunities. We envisioned that this second step could be provided by an enantioselective acylation of the corresponding *anti* diols (Scheme 2b). However, such organocatalytic KR of acyclic *anti* 1,3-diols[12] remains unprecedented because it faces massive challenges: 1) the high flexibility of the substrates and the lack of catalysts able to induce an efficient stereocontrol; 2) the potential formation of multiple side products and undesired isomers.

We assumed that such a challenging transformation could be achieved thanks to an additive Horeau amplification. It could result from a DoCKR process in which a first enantioselective esterification would be followed by a second acyl transfer on the major enantiomer (Scheme 2c). The produced diester and the recovered diol of opposite absolute configurations should both be obtained with a high level of enantioselectivity. The monoester fraction would constitute the sacrificial part of the amplifying process.



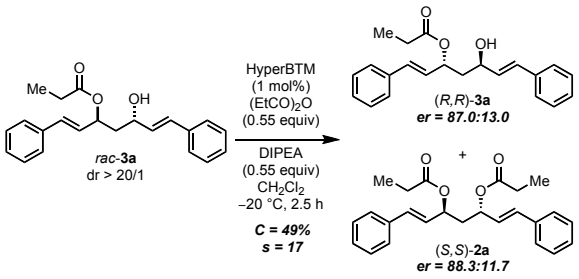
Scheme 2. (a) Classical approach to prepare enantioenriched acyclic *anti* 1,3-diols (b) DoCKR for acyclic racemic *anti* 1,3-diols. (c) Mechanistic scenario of the DoCKR.

We started our study with the C_2-symmetrical substrate **1a**, synthesized in only two steps (dr > 20:1). This compound displays two easy post-transformable C-C double bonds providing rigidity and possible interactions with the catalyst. Based on our previous works and deliberately avoiding any catalyst screening we selected the commercial available Smith's HyperBTM[13] as a promising chiral catalyst. A brief optimization of the reaction conditions (see supporting informations) led us to identify a combination of propionic anhydride with 1 mol% of HyperBTM as extremely efficient in terms of yield and selectivity. Indeed, under these standard conditions, diol **1a** was recovered in 41% yield (out of a maximum of 50%) and 99.6:0.4 er while diester **2a** was produced in 41% yield (out of a maximum of 50%) and 98.0:2.0 er. As expected, the small monoester fraction **3a** (6%) was obtained with a poor selectivity serving in the process as the sacrificial part (Scheme 3). Interestingly, the small initial amount of *syn* diol contaminating the racemic *anti* diol was also captured as its monoester. It is noteworthy that each fraction is easily separable by simple chromatography making this process easy to handle.



Scheme 3. Validation of the hypothesis and optimized conditions of the DoCKR.

To confirm the beneficial effect of the double enantioselective acylation, the KR of racemic monoester **3a** was conducted under similar conditions but with reduced amounts of anhydride and base (Scheme 4). As expected, the single enantioselective acyl transfer resulted in lower levels of selectivity and a *s* value[14] of 17. This value was brought up to 28 when the DoCKR process was performed onto related diol **1a** (Entry 1, Table 1). The additive Horeau amplification can then convert a reaction displaying a moderate intrinsic selectivity into a highly enantioselective synthetic methodology.



Scheme 4. KR of racemic monoester **3a**.

The scope of the DoCKR was then examined with racemic C_2-symmetrical 1,3-diols bearing π-systems in allylic or benzylic positions (Table 1). Excellent results were obtained for both

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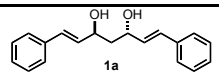
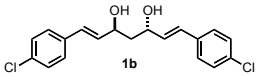
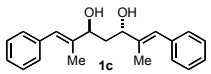
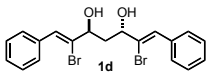
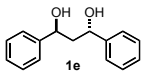
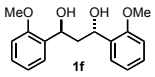
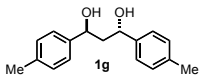
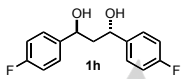
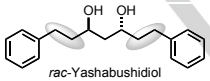
allylic diols (**1a-d**) and benzylic diols (**1e-h**) series. Indeed, diols were recovered in 40-46% yield in enantiopure form in many cases, which correspond to excellent *s* values between 15 and 73. Similar results were obtained for the diesters with yields > 40% and er > 97:3. Due to the symmetry of the substrates, it does not matter on which hydroxyl group, the first acylation happens. It seems reasonable to propose that the two successive acylation reactions on one enantiomer of the *anti* 1,3-diol occur approximately at the same kinetic rate. The efficiency and the scalability of this new method were demonstrated by running the reaction with racemic diol **1a** on a 3.5 g scale. Optically active diol **1a** (1.40 g) and diester **2a** (2.03 g) were obtained with comparable excellent yields and selectivities using a reduced amount of catalyst (0.5 mol%) (entry 1). In order to push further the limits, we examined the DoCKR of a diol without π-system nearby the reactive centers (entry 9). Racemic yashabushidiol was tested under the standard conditions giving a monoester and the corresponding diester with poor enantioselectivity but the recovered diol in 21% yield with very high er (> 99:1).

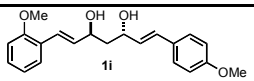
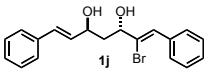
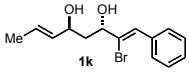
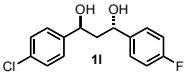
We expected that a significant step forward would be accomplished in term of synthetic potential if this methodology was applicable to unsymmetrical *anti* 1,3-diols. In such cases, the rates of the two successive acylation reactions might be significantly different leading to a more complex kinetic sorting. Different series of substrates were prepared and evaluated in acylative DoCKR: diversely substituted *anti* hepta-1,6-dien-3,5-diols (**1i-k**), *anti* 1,3-diarylpropan-1,3-diols (**1l-n**) and *anti* 1,5-diaryl-pent-1-en-3,5-diols (**1o-s**). With these three series, *s* values between 18 and 79 were obtained. High levels of enantioselectivity were reached with comparable yields for both the recovered diols and the diesters. The transformation tolerates heterocycles such as furan or thiophene derivatives (Table 2, entries 5, 6 and 11), as well as trisubstituted double bonds (Table 2, entries 2, 3, 9 and 10). Finally the DoCKR of *anti* 1,3-diol **1t**, presenting one benzylic alcohol and one secondary hydroxyl group without π-system at its proximity (e.g in allylic or benzylic position), was examined. The enantioselectivity of the recovered diol was not affected by this structural change remaining at a high level (99.5:0.5 er) while the er of its diester was slightly lower. Its *s* value (27 for **1t**) was quite similar to the unsaturated precursor **1o** (*s* = 29). This last example pinpoints the strong potential of the DoCKR process, able to overcome a challenging selective transformation.

Table 1. DoCKR of C_2-symmetrical 1,3-diols.[a]

Entry	*rac*-diol	Rec. diol[e] Yield (%)[b] (er)[c]	Diester[e] Yield (%)[b] (er)[c]	*s*[d]
1	 **1a**	40[f] (98.4:1.6)	41[f] (99.3:0.7)	28
2	 **1b**	40 (97.6:2.4)	40 (98.9:1.1)	16
3	 **1c**	43 (>99.9:0.1)	44 (99.6:0.4)	51
4	 **1d**	40 (97.1:2.9)	44 (98.3:1.7)	15
5	 **1e**	46 (98.7:1.3)	46 (98.1:1.9)	46
6	 **1f**	44 (>99.9:0.1)	40 (99.9:0.1)	60
7	 **1g**	43 (>99.9:0.1)	42 (97.4:2.6)	51
8	 **1h**	45 (>99.9:0.1)	45 (98.6:1.4)	73
9[g]	 *rac*-Yashabushidiol	21% (99.5:0.5)	19% (61.2:38.8)	7

[a] Typical experiment performed on 0.5 mmol of racemic diol under the standard conditions. [b] isolated yield. [c] determined by HPLC with chiral phase, for details see the supporting information section. [d] based on recovered diol. [e] dr > 20:1 in all cases. [f] Run on 3.5 g of racemic diol with 0.5 mol% of catalyst. [g] Monoester was also produced in 50% yield and 70.6:29.4 er.

Table 2. DoCKR of non-C_2-symmetrical 1,3-diols.[a]

Entry	*rac*-diol	Rec. diol[e] Yield (%)[b] (er)[c]	Diester[e] Yield (%)[b] (er)[c]	*s*[d]
1	 **1i**	38 (99.7:0.3)	43 (95.8:4.2)	22
2	 **1j**	38 (99.7:0.3)	43 (98.0:2.0)	22
3	 **1k**	34 (>99.9:0.1)	33 (88.5:11.5)	21
4	 **1l**	41 (97.7:2.3)	47 (96.5:3.5)	18

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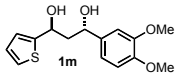
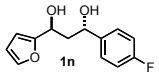
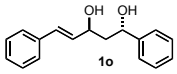
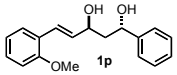
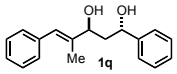
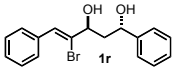
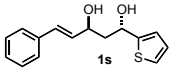
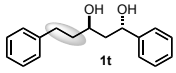
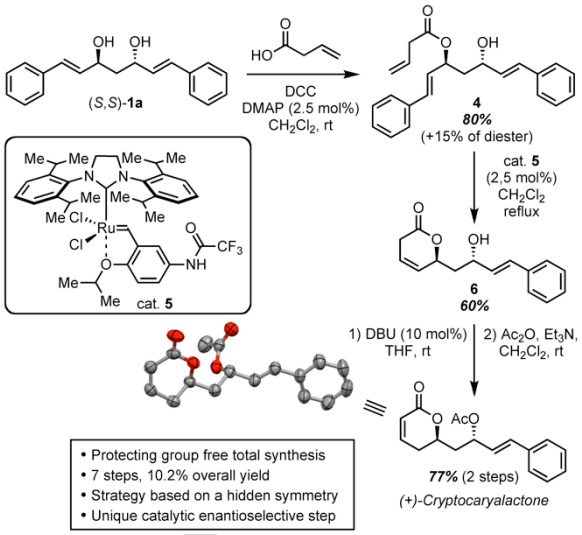
5	 1m	43 (99.1:0.9)	47 (98.5:1.5)	30
6	 1n	49 (97.4:2.6)	38 (98.2:1.8)	79
7	 1o	39 (99.9:0.1)	40 (98.2:1.8)	29
8	 1p	39 (99.7:0.3)	43 (96.2:3.8)	24
9	 1q	40 (99.6:0.4)	40 (97.9:2.1)	25
10	 1r	41 (>99.9:0.1)	43 (98.4:1.6)	39
11	 1s	36 (>99.9:0.1)	38 (90.3:9.7)	24
12	 1t	41 (99.5:0.5)	37 (86.9:13.1)	27

[a] Typical experiment performed on 0.5 mmol of racemic diol under the standard conditions. [b] isolated yield. [c] determined by HPLC with chiral phase, for details see the supporting information section. [d] based on recovered diol. [e] dr > 20:1 in all cases.

We decided to apply this methodology to the total synthesis of (+)-cryptocaryalactone,[15] a natural germination inhibitor (Scheme 5). The acylation reaction of the virtually enantiopure diol **1a** with vinylacetic acid under classical conditions [DCC, DMAP cat., CH_2Cl_2, rt] gave monoester **4** (80%) accompanied by a small amount of diester (15%). The formed triene **4** then underwent a ring-closing metathesis reaction using the highly active catalyst **5**[16] to afford lactone **6**. Migration of the internal double bond under DBU catalysis[17] followed by an acylation reaction afforded (+)-cryptocaryalactone.[18] This hidden symmetry strategy[19] represents the shortest synthesis of this target reported to date.[20] Additionally, no protecting group was required for this synthesis,[21] which employed a unique organocatalytic enantioselective step.[22]

In conclusion, we described a highly enantioselective synthetic separation of acyclic *anti* 1,3-diols, which are ubiquitous structural motifs in nature. This development was made possible by the design of a synergistic double catalytic kinetic resolution (DoCKR) and by a full exploitation of the additive Horeau principle. This efficient, general and scalable method using an



Scheme 5. Total synthesis of (+)-cryptocaryalactone.

organocatalyzed acylation (0.5 – 1 mol% catalyst loading) gives an easy access to both enantiomers of a given acyclic *anti* 1,3-diol with high yields and enantioselectivities. The methodology was successfully applied to C_2-symmetrical substrates and then further extended to the challenging and unprecedented cases of non-C_2-symmetrical *anti* 1,3-diols. To the best of our knowledge, the use of such non-symmetrical substrates bearing pre-existing stereocenters in amplified systems was not reported so far.

Finally, the effectiveness of the DoCKR was applied to an efficient total synthesis of (+)-cryptocaryalactone using a single catalytic enantioselective step. This flexible approach leads to both enantiomers, which are useful in total synthesis of natural product containing stereocenters with unassigned absolute configuration. All in all, we strongly believe that the concept of DoCKR could be of broader utility for the synthetic community and potentially transposed to other bifunctional substrates.

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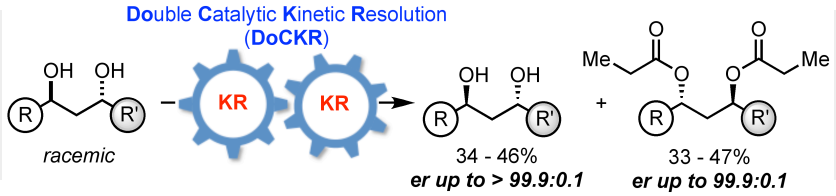

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