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Efficient Chemoenzymatic Dynamic Kinetic Resolution of 1-Heteroaryl Ethanols

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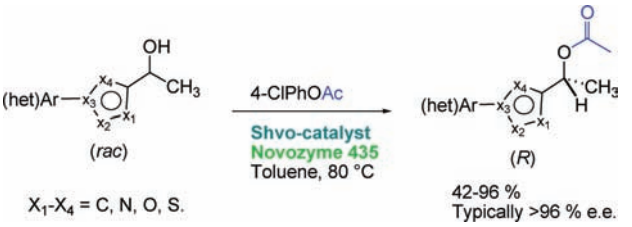

The scope and limitation of the combined ruthenium-lipase induced dynamic kinetic resolution (DKR) through *O*-acetylation of racemic heteroaromatic secondary alcohols, i.e., 1-heteroaryl substituted ethanols, was investigated. After initial screening of reaction conditions, *Candida antarctica* lipase B (Novozyme 435, N435) together with 4-chloro-phenylacetate as acetyl-donor for kinetic resolution (KR), in conjunction with the ruthenium-based Shvo catalyst for substrate racemization in toluene at 80 °C, enabled DKR with high yields and stereoselectivity of various 1-heteroaryl ethanols, such as oxadiazoles, isoxazoles, 1*H*-pyrazole, or 1*H*-imidazole. In addition, DFT calculations based on a simplified catalyst complex model for the catalytic (de)hydrogenation step are in agreement with the previously reported outer sphere mechanism. These results support the further understanding of the mechanistic aspects behind the difference in reactivity of 1-heteroaryl substituted ethanols in comparison to reference substrates, as often referred to in the literature.

Introduction

Enantiomerically pure 1-heteroaryl ethanols **1**, wherein the heteroaryl moiety **Q** constitutes five-membered nitrogen-containing heteroaromatics, are of broad general interest as synthetic intermediates, metal chelators and ligands, chiral auxiliaries, and potential drug leads or scaffolds.

The heteroatoms of **1** entail and enrich the molecule with requisite properties for the interaction with proteins, for the ability of it to coordinate to metals, and for the prospect of the heteroaromatic part **Q** to function as a masked equivalent of other functional groups. Furthermore, the asymmetry of **1** is essential for its use as a chiral auxiliary and is often desirable for the selective and optimal interaction with proteins, e.g., receptors and enzymes. Compounds **1** are for example chiral 1,2,4-triazoles, in which the heterocycle simultaneously is serving as a masked amino group of primary amines[1,2] and amino acids,[3] which have been used as chiral inducers in stereoselective alkylations. Five-membered heterocycles are furthermore present in a plethora of compounds, both natural and synthetic in origin, that bear well-defined biological activities.[4−18]

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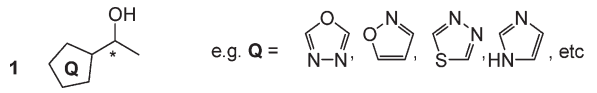
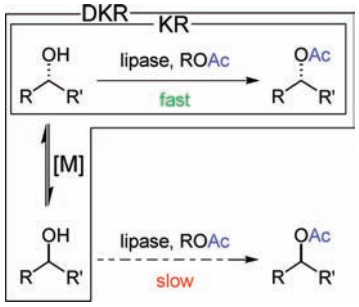


FIGURE 1. **Q** is a five-membered heterocyclic ring.

Thus, heteroaryl ethanols **1** constitute a highly interesting small molecular scaffold in drug research structural optimization. Synthetic approaches often are limited to the use of a chiral starting material,[19−22] if not on tedious chiral separation alone. General methodologies for the construction of various chiral heterocyclic compounds **1** from either achiral or racemic precursors are therefore desired. Previous reports on the former include stereoselective reductions[5,20,23−30] and the use of biocatalysts in the form of either isolated enzymes or whole cells.[25,31−34] Earlier literature describing the latter comprise resolution by chromatographic separation,[35] enzymatic deracemization,[36] and kinetic resolution (KR) by selective oxidation of one of the enantiomers.[37,38] To our knowledge, only two reports on successful KR through lipase-catalyzed acylation of racemic alcohols **1** have been published, both of them including a thiazole as the heterocyclic moiety **Q**.[39,40] Reports on analogous KRs, where **Q** of **1** is represented by benzene[41−43] or by heterocycles such as furan,[42] thiophene,[44,45] and pyridine,[46] are more frequent. The fact that one enantiomer can be obtained in only a 50% maximum yield from the racemate by any conventional KR has brought much attention to the concept of dynamic kinetic resolution (DKR),[47] where a theoretic yield of 100% can be reached. In DKR, the enantiomer discriminated by the irreversible KR process is simultaneously racemized, or inverted, by a second process run *in situ*. Since the second process is in equilibrium with the first, a full overall conversion is achievable (Scheme 1).

SCHEME 1. DKR versus KR



The DKR of racemic secondary alcohols, involving a lipase for the KR process,[48−50] was first proven possible by Williams and co-workers[51] when combined with racemization mediators based on the metals aluminum, iridium, and rhodium. A significant improvement was later accomplished through the pioneering work by Bäckvall's group demonstrating that the ruthenium racemization precatalyst **2**, commonly known as the "Shvo catalyst", can be well combined with lipases in DKRs.[52−54]

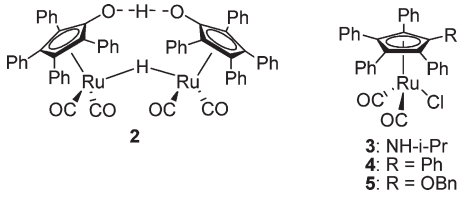


FIGURE 2. Ruthenium precatalysts.

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Other highly efficient ruthenium precatalysts include **3** and **4**.[55−57] Recently, Park et al. reported on the robust racemization catalyst **5**.[58] In addition, Trauthwein et al. identified a stable racemization catalyst, constituting a $[Ru(cymene)Cl_2]_2$ complex bearing chelating aliphatic diamines.[59] These and others have been recently reviewed.[60,61] Mechanistic studies by the groups of Casey et al. and Lledós et al.[62a,b] showed compelling evidence for a concerted hydrogen transfer mechanism (*vide infra*).

Encouraged by the recent advancements in DKR of secondary alcohols, we envisioned this methodology as a viable approach to chiral alcohols **1**, starting from the corresponding racemic mixtures. In this paper, we wish to report our results on DKR, employing a lipase in combination with the Shvo catalyst (**2**), with focus on racemic heterocyclic alcohols encompassed by **1**, including substrates hitherto not or rarely found in literature. Since such substrates are not as readily accessible as the typical model substrates employed in exploratory DKR, we took advantage of a computational model for the design of substrates and for an estimate of their performance in the DKR. The correlation between these findings and the experimental results is discussed.

Results and Discussion

Synthesis of Racemic 1-Heteroaryl Ethanols. Initially, we desired a set of representative heterocyclic racemic substrates as well as selected *O*-acetylated derivatives thereof as analytical references. In each case, the synthetic route of choice was much dictated by the adherent heterocycle as described below.

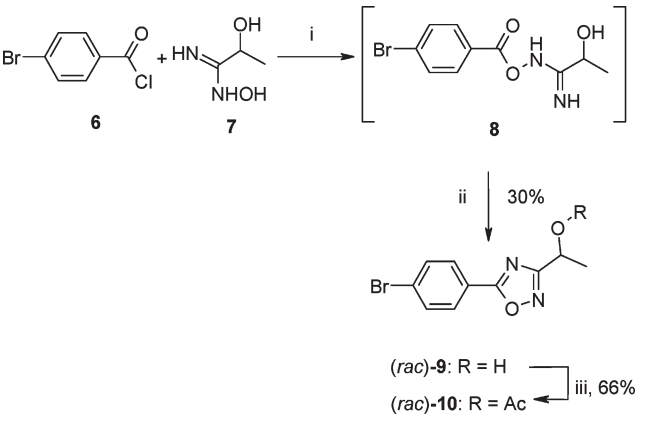
The 5-aryl substituted 1,2,4-oxadiazole (*rac*)-**9** was synthesized by selective *O*-benzoylation of *N*-hydroxy-amidine **7**, followed by ring closure of the acyclic intermediate **8** by heating in ethanol as described in Scheme 2. The corresponding racemic acetate (*rac*)-**10** was subsequently obtained by conventional acetylation.

As independent enantiomerically pure reference materials with known absolute configuration, the chiral 3-aryl substituted 1,2,4-oxadiazole (*S*)-**13** and the corresponding acetylated derivative (*S*)-**14** were synthesized from L-(+)-lactic acid as shown in Scheme 3. Benzonitrile **11** was first converted to *N*-hydroxy-amidine **12** by treatment with hydroxyl amine in ethanol, followed by DCC-mediated coupling with L-(+)-lactic acid and subsequent ring closure to yield (*S*)-**13**. Under these conditions, no racemization of (*S*)-**13** or precursors could be noted. Oxidation of (*S*)-**13** with PCC yielded ketone **15**, which was reduced back with sodium borohydride to give (*rac*)-**13**. The corresponding acetates (*S*)-**14** and (*rac*)-**14** were obtained by acetylation of (*S*)-**13** and (*rac*)-**13**, respectively.

The 1,3,4-oxadiazole alcohol (*rac*)-**18** was conveniently obtained by displacing the chloride of (*rac*)-**16** with potassium acetate in DMF, followed by hydrolysis of the formed acetate (*rac*)-**17** as described in Scheme 4. The starting material (*rac*)-**16** was prepared from 3-chlorobenzohydrazide in two steps.[63] The 5-(het)aryl substituted isoxazoles (*rac*)-**21** and (*rac*)-**22** were synthesized by treatment of the corresponding commercially available aldehydes **19** and **20**, respectively, with methyllithium.[63]

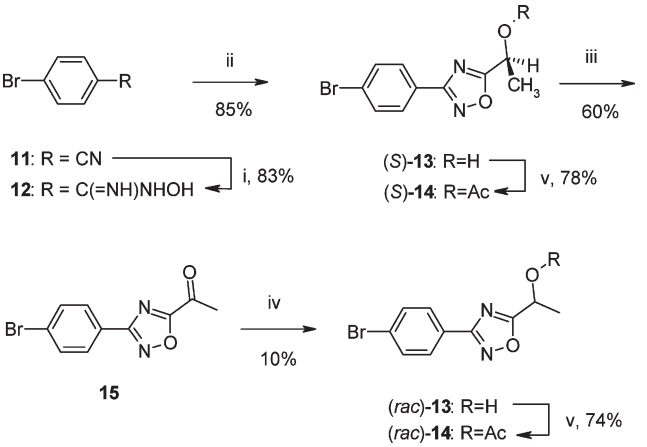
Oxime **24** was prepared by treatment of aldehyde **23** with hydroxyl amine (Scheme 5).[64] Pyridyl oximes **25**−**27** were commercially available. Hydroximoyl chlorides **28**−**31** were

SCHEME 2. Synthesis of 5-Aryl Substituted 1,2,4-Oxadiazoles[a]



[a]Reagents and conditions: (i) pyridine, DCM, 0 °C to rt; (ii) reflux in EtOH; (iii) AcCl, 10 mol % HOBt, TEA, DCM, 0 °C to rt.

SCHEME 3. Synthesis of 3-Aryl Substituted 1,2,4-Oxadiazoles from L-(+)-Lactic Acid[a]



[a]Reagents and conditions: (i) $H_2NOH \cdot HCl$, NaOH, reflux in EtOH; (ii) L-(+)-lactic acid, HOBt (10 mol %), DCC, DMSO, rt, then reflux in EtOH; (iii) PCC, DCM, rt; (iv) $NaBH_4$, THF, rt; (v) AcCl, HOBt (10 mol %), triethylamine, DCM, 0 °C to rt.

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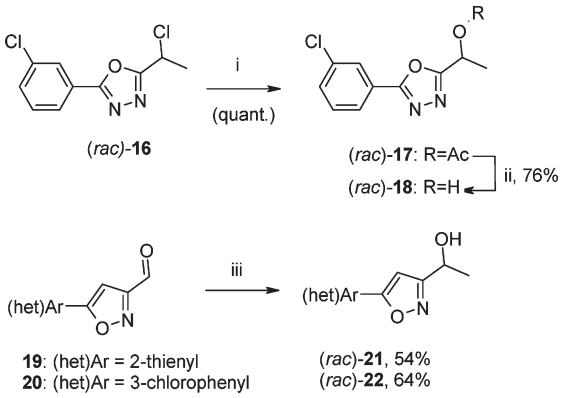
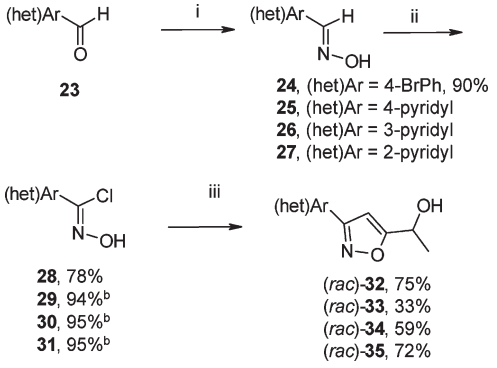
SCHEME 4. Synthesis of 1,3,4-Oxadiazoles and 5-(Het)aryl Substituted Isoxazoles[a]



[a]Reagents and conditions: (i) KOAc, DMF, rt; (ii) KOH, MeOH, rt; (iii) MeLi, THF, rt.

SCHEME 5. Synthesis of 3-Aryl Substituted Isoxazole Derivatives[a]

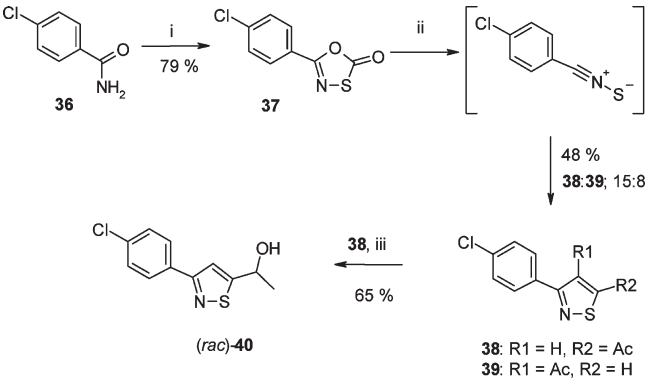


[a]Reagents and conditions: (i) $H_2NOH \cdot HCl$, H_2O, EtOH; (ii) $BnN^+Me_3 ICl_4^-$, DCM; (iii) 3-butynol, Et_3N, EtOH. [b]Isolated as the HCl salt.

synthesized by chlorination of oximes **24**−**27** according to the procedure of Kanemasa et al.[65] The corresponding nitrile oxides, generated *in situ* by treatment of these with triethylamine, underwent cycloaddition with 3-butynol to furnish the 3-(het)aryl substituted isoxazoles (*rac*)-**32** to (*rac*)-**35**, respectively.[66]

The 3-aryl substituted isothiazole (*rac*)-**40** was prepared starting from amide **36** as described in Scheme 6.[43,45] Initial treatment with chlorocarbonylsulfenyl chloride generated oxathiazolone **37** in good yield. 1,3-Dipolar cycloaddition of the corresponding unstable nitrile sulphide, obtained by thermal decarboxylation of **37**, with 3-butyn-2-one gave a mixture (73:27, respectively) of regioisomers **38** and **39**.[44] These were easily separated by chromatography, and ketone **38** was subsequently reduced with sodium borohydride to yield alcohol (*rac*)-**40**. Attempted cycloaddition employing the relatively more electron-rich 3-butyn-2-ol as reagent resulted in formation of 4-chlorobenzonitrile as the only isolable product.

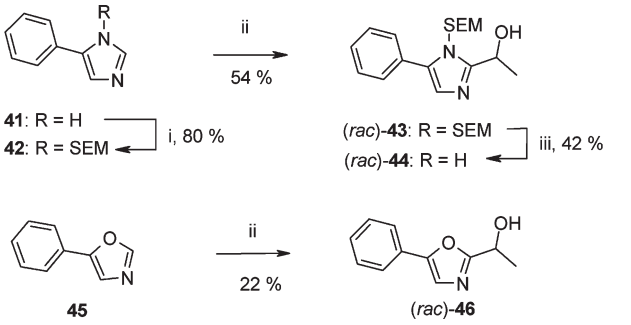
SCHEME 6. Synthesis of a 3-Aryl Substituted Isothiazole[a]



[a]Reagents and conditions: (i) ClCOSCl, toluene, 100 °C; (ii) but-3-yn-2-one, MW irradiation, 120 °C; (iii) $NaBH_4$, THF.

Oxazole (*rac*)-**46** and imidazole (*rac*)-**43** were obtained by lithiation of the corresponding unsubstituted derivatives **45** and **42**, respectively, followed by trapping with acetaldehyde as described in Scheme 7. The SEM group, employed to direct lithiation at the imidazole ring of **42**, was removed by treatment with TBAF to yield (*rac*)-**44**.[46]

SCHEME 7. Synthesis of Imidazoles and Oxazole Derivatives[a]



[a]Reagents and conditions: (i) NaH, SEM-Cl, DMF; (ii) *n*-BuLi, THF, −78 °C, then acetaldehyde, −78 °C to rt; (iii) TBAF, THF, rt.

Evaluation of Lipases and Acyl Donors for KR. The commercially available immobilized lipases *Candida antarctica* lipase B (Novozyme 435, N435),[67] *Mucor miehei* (MM),[68] *Pseudomonas cepacia* (PC),[41] and *Candida cylindracea* (CC)[69] have all been used in KR of substrates in which the sterically less demanding substituent, in analogy to **1**, is composed of a methyl group and were therefore considered as suitable candidate lipases. The three acyl donors isopropenyl acetate **47**, 4-chlorophenyl acetate **48**, and 3-acetoxypyridine **49** were chosen for evaluation (Figure 3).

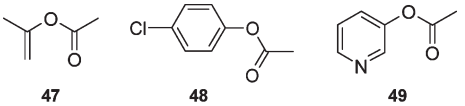


FIGURE 3. Acyl donors.

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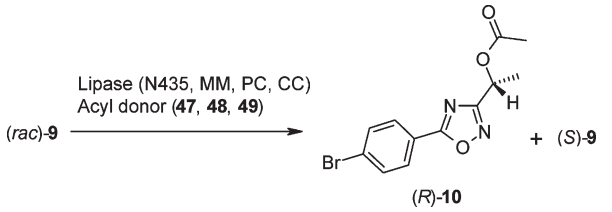
The former two were chosen because of their wide use in KRs and DKRs, respectively, and the latter because of an early report by Kitajima et al. on the successful use of heterocyclic acyl donors in KRs.[70] We reasoned that the use of **49** could be advantageous due to its relatively higher water solubility and polarity as compared to that of **48**, which is occasionally difficult to separate from the product and in addition generates a toxic side product, *p*-chlorophenol.[53,71] Screening of the candidate lipases in all combinations with the acyl donors **47**−**49** in KR of the 1,2,4-oxadiazole (*rac*)-**9** as substrate in toluene at 30 °C was performed (Scheme 8, Figures 4 and 5).

SCHEME 8. Kinetic Resolution of (*rac*)-9 by Lipase Catalysed Acetylation[a]



[a]Reagents and conditions: (*rac*)-**9** (0.10 mmol/mL), lipase (30 mg/mmol of (*rac*)-**9**), acyl donor (2.0 equiv), toluene, 30 °C.

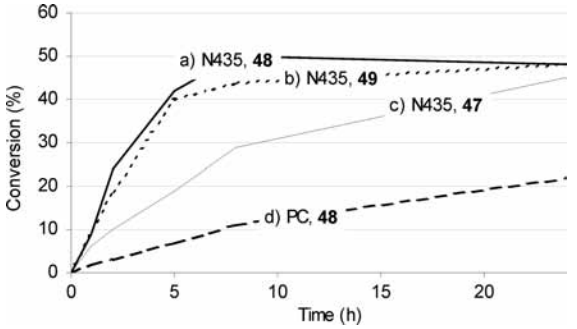


FIGURE 4. Substrate conversion profiles in KR of (*rac*)-**9** utilizing the following combinations of lipase/acyl donor: (a) N435/**48**; (b) N435/**49**; (c) N435/**47**; (d) PC/**48**.

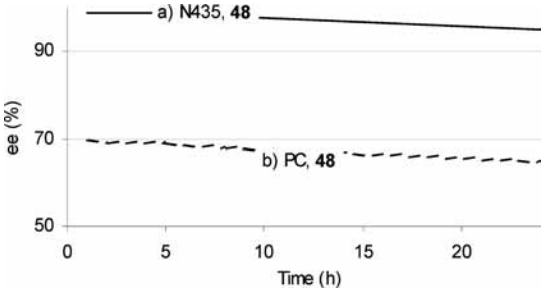


FIGURE 5. Product (*R*)-**10** enantiomeric excess profiles in KR of (*rac*)-**9** using the following combinations of lipase/acyl donor: (a) N435/**48**; (b) PC/**48**.

N435 proved to be the most suitable lipase irrespective of the acyl donor employed, with an E-value greater than 200.[68,69] In comparison, the E-value for PC was only 6 (Figures 4 and 5).

In this application, MM and CC proved to be of limited use, as only trace amounts of the product could be detected despite prolonged reaction times. **48** and **49** were found to be comparable as acyl donors, and both were slightly more efficient, in terms of reaction rate, as compared to **47**. In order to confirm the efficiency of N435 on a preparative scale, (*rac*)-**9** was subjected to KR by employment of this lipase in combination with **47** as acyl donor for 72 h in toluene at ambient temperature. (*S*)-**9** and (*R*)-**10** were upon isolation each obtained in a 49% yield, each with a high optical purity.

Dynamic Kinetic Resolution. As guided by the results from the KR study, initial DKR experiments with (*rac*)-**9** (0.10 mmol/mL solvent) were conducted using N435 (3.0 mg/mL) as the selected lipase at 70 °C in toluene, in the presence of 2.0 mol % of the Shvo catalyst (**2**) and 3.0 equiv of the acyl donor (**48** or **49**). A 50% conversion of the substrate was observed in less than 3 h using either **48** or **49** as acyl donor. In the former case, a 72% conversion was achieved after 48 h, whereas in the latter case the reaction never got beyond 50% conversion even after 120 h. These results indicate a deactivation of the Shvo catalyst (**2**) when employing **49** as acyl donor. We speculate that **49** in itself or, alternatively, pyridin-3-ol formed from **49** may be responsible for this deactivation by coordination to ruthenium. The results are furthermore indicative of a fast initial consumption of the *R*-alcohol by acetylation and of a comparably significantly slower racemization process. In order to get more comparable kinetics between these two processes, the reaction temperature and the stoichiometry of the racemization catalyst were increased to 80 °C and 5.0 mol %, respectively, while the amount of the lipase N435 was diminished to 2.0 mg/mL. The 4-chlorophenol, generated when using **48** as the acyl donor, tended to coelute with the desired acetylated products upon purification by chromatography. We solved this issue by carrying out an alkaline wash (1.0 M NaOH) of the crude product prior to further purifications. These reaction settings and this workup procedure were used in all further experiments, which are summarized in Tables 1 and 2.[72]

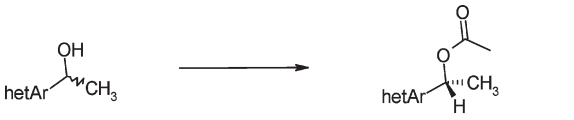
From the results summarized in Table 1, it can be concluded that N435 is a highly stereoselective biocatalyst with high acceptance for substituted heterocyclic substrates. In general, the *R*-enantiomers of the racemic substrates in this study were selectively and effectively acetylated, as indicated by yields close to 50% or greater, with high enantiomeric purities of the products. One outstanding exception is represented by the imidazole (substrate **44**, entry 16), where no acetylated product (*R*)-**62** could be detected. Interestingly, the corresponding *N*-SEM substituted imidazole (*rac*)-**43** proved to be an excellent substrate (entry 15). The absolute stereochemistry of the product (*R*)-**14** (entry 1) was confirmed by comparing with independently synthesized (*S*)-**14** and (*rac*)-**14** (Scheme 3) and thereby found to be in accordance with

(70) Keumi, T.; Hiraoka, Y.; Ban, T.; Takahashi, I.; Kitajima, H. *Chem. Lett*. **1991**, 1989–92.

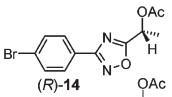
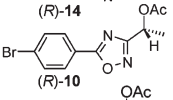
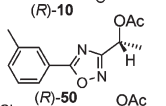
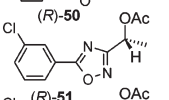
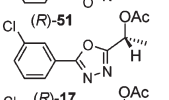
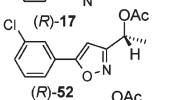
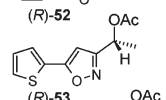
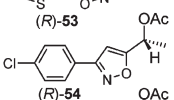
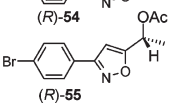
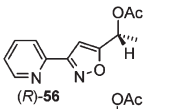
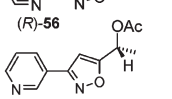
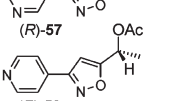
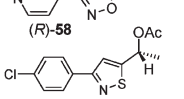
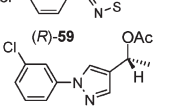
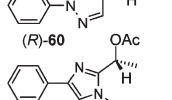
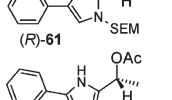
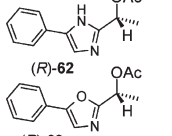
(71) Verzijl, G. K. M.; de Vries, J. G.; Broxterman, Q. B. *Tetrahedron: Asymmetry* **2005**, *16*, 1603–1610.

(72) Three equivalents of acyl donor in the DKR were used due to the properties of the pyridine based donor **49**. All subsequent reactions with **48** were, for ease of comparison, also run with 3 equiv of donor instead of 2 equiv, as used in the KR, which nevertheless allowed determining the important relative differences between various substrates.

TABLE 1. DKR of Racemic 1-Heteroaryl Ethanols[a]



(*R*)-**10**, (*R*)-**14**, (*R*)-**17**, (*R*)-**50-63**

Entry	Product	Time (h)	Conv[b] (%)	Yield LC[b] [Isolated] (%)	ee[b] (%)
1	 (*R*)-**14**	48	87	47	>96
2	 (*R*)-**10**	48	93	43 [43]	96
3	 (*R*)-**50**	48	98	59 [39]	94
4	 (*R*)-**51**	48	97	57 [39]	95
5	 (*R*)-**17**	72	62	60 [47]	88
6	 (*R*)-**52**	24	96	60 [43]	98
7	 (*R*)-**53**	24	84	49 [44]	>96
8	 (*R*)-**54**	24	98	96 [69]	>98
9	 (*R*)-**55**	24	99	64 [53]	>98
10	 (*R*)-**56**	24 48[c]	100 100	54 82 [57]	>99
11	 (*R*)-**57**	48	59	48 [36]	>98
12	 (*R*)-**58**	48	57	55 [37]	>98
13	 (*R*)-**59**	24	98	50[33]	>98
14	 (*R*)-**60**	24	100	80 [72]	95
15	 (*R*)-**61**	24 48[c]	100 100	81[73]	>98
16	 (*R*)-**62**	48	[d]	[d]	[d]
17	 (*R*)-**63**	24 48[c]	54 60	42[40]	>98

[a]Reaction conditions: substrate (0.1 mmol/mL), acyl donor **48** (3.0 equiv), Shvo catalyst (**2**) (0.05 equiv), lipase N435 (2.0 mg/mL), toluene, 80 °C under argon. [b]Determined by chiral HPLC. Entry 1 is estimated as a result of uncomplete baseline separation. [c]2,4-Dimethyl-3-pentanol (1.0 equiv) was added after 24 h. [d]No reaction.

the predictive rule stating a preference of the lipase to accommodate the *R*-enantiomer.[73]

Although the KR component of the DKR of these heterocyclic substrates is a robust process, the indispensable ruthenium-catalyzed racemization was found to be more substrate-dependent in contrast to typical model substrates and thus warrants focus in the discussion of the obtained results. The outcome of the experiments may be divided into three categories:

(1) High conversion and high yield, which is indicative of a well working racemization with no or minimal competing side reactions. The 3-aryl isoxazole (entry 8) and the 1-aryl pyrazole (entry 14) represent heterocycles belonging to this group of substrates.

(2) High conversion and medium yield (poor mass balance), as observed for several substrates (entries 1−4, 6, 7, 9, 10, and 13), suggests a significant competing side reaction. Ketones, corresponding to the respective secondary alcohol substrates, were detected as the major byproduct (entries 6, 9, 10, 13, 15). It is known that ketones can be formed by ruthenium-catalyzed dehydrogenation of secondary alcohols and that this reaction can be suppressed by an added hydride donor, such as a sacrificial alcohol (e.g., 2,4-dimethyl-3-pentanol), or under a hydrogen atmosphere.[74,75] Indeed, addition of 2,4-dimethyl-3-pentanol to the reaction mixture of isoxazole (*rac*)-**35** (entry 10) at the 24 h time point (100% conversion, 54% yield) resulted in improved yield and mass balance at the 48 h time point (100% conversion, 82% yield).

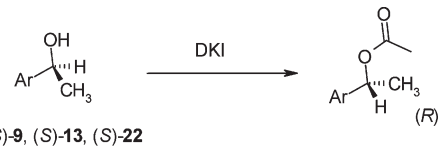
These results are in accordance with a mechanism in which ruthenium-catalyzed dehydrogenation is highly favored over reduction of the intermediate ketone, where the racemization is occurring under ruthenium catalysis (Scheme 9). This dehydrogenation/reduction balance, however, may be altered by the intervention of a hydride donor to enable or improve a DKR as shown in the example above. The substrates in this category are seemingly either favoring the dehydrogenation or preventing the corresponding reduction.

(73) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.

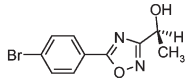
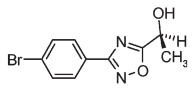
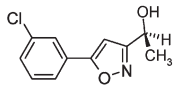
(74) Edin, M.; Steinreiber, J.; Bäckvall, J.-E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5761–5766.

(75) Pamies, O.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2001**, *343*, 726–731.

TABLE 2. DKI of *S*-Alcohols[a]

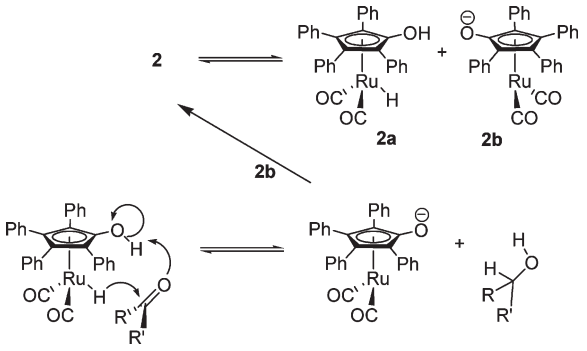


(*S*)-**9**, (*S*)-**13**, (*S*)-**22**

Entry	Substrate	Time (h)	Conv[b] (%)	Yield LC[b] (%)	ee[b] (%)
1	 (*S*)-**9**	72	99	10	72
2	 (*S*)-**13**	120	71	7[c]	65[c]
3	 (*S*)-**22**	66	92	10	>99

[a]Reaction conditions: see Table 1. [b]Determined by chiral HPLC. [c]The *S*-acetate was obtained as major isomer.

SCHEME 9. Catalyst Activation (top) and Hydrogen Transfer (below)



(3) Medium conversion and medium yield (with concurring good mass balance) is the expected result in the case of a functional and stereoselective acetylation reaction, but with a sluggish racemization process and without significant dehydrogenation. The outcome of the reaction is thus similar to what is expected from a KR. 1,3,4-Oxadiazole (*rac*)-**18** (entry 5), oxazole (*rac*)-**46** (entry 17), and the 3- and 4-pyridyl substituted isoxazoles (*rac*)-**34** and (*rac*)-**33** (entries 11 and 12, respectively) are substrates that are more or less inert to catalysis by **2**. Accordingly, the corresponding *S*-alcohols were the major components detected besides the desired *R*-acetates in these cases. If the ruthenium catalyst effectively mediates racemization of the alcohol, it should be independent of the optical purity of scalemic (*S*-configured) substrate. Therefore, based on any given DKR of the present study, the outcome of the reaction should be comparable in the case of a dynamic kinetic inversion (DKI), i.e., where an *S*-alcohol, instead of the corresponding racemate, is converted to the corresponding *R*-acetate. Thus, three substrates, where doubt existed on whether or not a true DKR took place (entries 1, 2, and 6, Table 1), were selected for DKI experiments (Table 2). It is interesting to compare the results obtained from the 5-aryl substituted 1,2,4-oxadiazole (*S*)-**9** (entry 1) with those from the 3-aryl substituted regioisomer (*S*)-**13** (entry 2). Although (*S*)-**9** underwent DKI, albeit in a low yield and with poor ee, no *R*-acetate could be obtained from (*S*)-**13** despite a prolonged reaction time. Instead, under these forcing conditions, the *S*-acetate was formed in enantiomeric excess. DKI of isoxazole (*S*)-**22** resulted in a low yield of the *R*-acetate, but with high ee (entry 3). The low mass balance in this case resulted from pronounced ketone formation. This low racemazation is nevertheless enough to drive a DKR; see Table 1, entry 6.[76]

The results summarized in Tables 1 and 2 reveal structural features that are of importance for the success of the racemization and thereby for the DKR of heterocyclic substrates. It is clear, as expected, that the nature of the heterocycle, to which the chiral center of the ethanol residue is attached, is of importance. Its close proximity to the hydroxyl group permits electronic interaction, as well as a possibility of intramolecular complex formation, with any of the intermediates belonging to the catalytic cycle of the racemization. For example, by substituting the isoxazole (entry 8, Table 1) for an isothiazole ring (entry 13, Table 1), a significant drop in yield (from 96% to 50%) is observed due to increased ketone formation. A similar observation is made for the regioisomeric isoxazole (entry 6, Table 1) where the adjacent heteroatom is oxygen and not nitrogen. Interestingly, various remote structural features were also noted to affect the racemization: the presence of a remote bromo substituent has a negative effect as compared to a chloro substituent (compare entries 8 and 9, Table 1). A remote 3- or 4-pyridyl substituent blocks racemization as well as dehydrogenation, while a remote 2-pyridyl substituent allows dehydrogenation of the substrate (compare entries 10−12, Table 1). In the latter case an effective DKR is accomplished by the addition of 2,4-dimethyl-3-pentanol.

Calculations

Inspired by and based on the mechanistic work by Casey's group and Lledós et al.,[62a,b] we believed our substrates to fit the concerted hydrogen transfer model (Scheme 9). At the same time, we envisioned a crude predictive model for substrate activity, which yet allowed a good approximation of the relative energies at the transition state of the transfer hydrogenation step. To accomplish this, we truncated the catalyst by replacing the phenyl groups with hydrogens (Figure 6) and calculated, for comparison, two examples with the complete catalyst.[77,78]

(76) When using substrate **22** with the more recent catalyst **4** developed by Bäckvalls group,[57] no racemization at all was observed after 24 h at room temperature. Private communication from Prof. J. E. Bäckvall.

(77) For verification and reference sake, we made test calculations with the phenyls present and found that the nature of the intermediates and the transition state does not change and the activation energy was just slightly increased (approximately 2 kcal/mol). We believe that when comparing different ligands of similar size as our substrates, the relative difference will not be significant.

(78) Calculations where performed using the Jaguar program (v7.5) from Schrodinger Inc. using the B3LYP functional and the lacvp** basis set. The relative energies includes solvent effects using benzene and the PBF approximation. All structures are fully optimzed (in gas phase) and characterized using Hessian calculation and normal-mode analysis. All reported relative energies includes entropy effects and solvent effects.

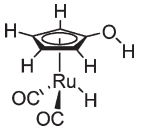


FIGURE 6. "Truncated" catalyst.

We then optimized the key intermediates and the transition state and computed the relative energies (Figure 7) of the typical (de)hydrogenation step (Table 3).

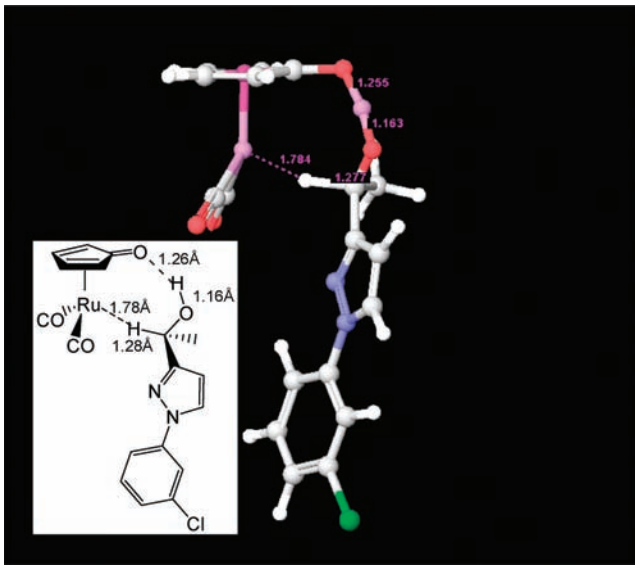


FIGURE 7. The transition state of the substrate in entry 14. Two hydrogen atoms migrate from the alcohol in a concerted way. Bond distances in Å.

TABLE 3. Calculations on Relative Hydrogenation Energies

entry	Table [1] entry	time[a] (h)	conv[a] (%)	ee[a] (%)	ΔE* (kcal)
1	5	72	62	88	17.2
2	12	48	57	98	16.7
3	8	24	98	98	15.1
4	14	24	100	95	12.9

[a]For reaction conditions, see Table 1.

The initial step of the mechanism involves coordination of the alcohol to the Ru(0) complex for all four substrates. The subsequent transition state for the formation of the corresponding ketone is believed to be a concerted oxidative transfer of two hydrogen atoms, one to the ruthenium atom (resulting in the formation of a hydride) and the other to the oxygen atom of the alcohol substrate (Figure 7). This "outer-sphere" mechanism has been reported before.[62b] In comparison to the conversions obtained experimentally, an acceptable correlation with the respectively calculated activation energies can be seen. For example, the substrate in entry 4 has a calculated activation energy of 12.9 kcal/mol, with a corresponding full conversion with 95% ee in the DKR, in comparison to the substrate in entry 1, which has a calculated activation energy of 17.2 kcal/mol and only 62% conversion experimentally. Hence, as also can be seen in entries 2 and 3, the trend of a low conversion in correlation to a relatively high activation barrier is emerging. Although absolute predictions cannot be made, the corresponding calculation may be used for predicting a qualitative outcome of a DKR for a given substrate.

Conclusion

In summary, we have demonstrated efficient DKR of a range of substituted heterocyclic racemic ethanols, hence extending the tool box for synthesis of valuable chiral substrates and intermediates. As of now, the reaction conditions are limited to the first generation Bäckvall-type of system, employing Novozyme, the Shvo catalyst, and 4-chlorophenyl acetate. In addition, we have presented theoretical data in the form of density functional calculations. The results therefrom are in alignment with the concerted hydrogen transfer mechanism proposed by Lledós, Ujaque, and Comas-Vives and supports the outcome of the experiments.

Experimental Section

General. General experimental details, suppliers, and experimental procedures for the synthesis of novel compounds are included in Supporting Information.

General Procedure for DKRs (Tables 1 and 2). To a glass vial equipped with a stirring bar were added the substrate (0.50 mmol), acyl donor **48** (0.21 mL, 1.5 mmol), Shvo catalyst **2** (0.027 g, 0.025 mmol), and N435 (10 mg) followed by toluene (5.0 mL). After having been swept with argon, the vial was closed, and the mixture was stirred while being heated in an aluminum block kept at 80 °C. Analytical samples were taken at every multiple of 24 h. The reaction was interrupted when the conversion of the substrate was >50% as judged by HPLC peak area comparison with an initial sample taken at 0 h, or after 120 h irrespective of the conversion at that time. The reaction mixture was then diluted with 2-propanol to 50.0 mL. From this mixture was decanted 1.00 mL, which was further diluted to 3.50 mL with 2-propanol in order to get an analytical sample from which the reaction yield and the enantiomeric excess were determined by chiral HPLC analysis, by comparison with references. The remaining volume was filtered through Celite before concentration *in vacuo*. The obtained residue was then redissolved in dichloromethane. This solution was washed with 1.0 M NaOH and once with brine before drying (Na_2SO_4). The residue obtained upon concentration *in vacuo* was purified by silica gel flash chromatography using as eluent either a gradient from *n*-hexane to *n*-hexane/dichloromethane:ethyl acetate, from *n*-heptane to *n*-heptane/ethyl acetate, or from dichloromethane to dichloromethane/methanol or a corresponding suitable isocratic mixture.

(1*R*)-1-[5-Phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-yl]ethyl acetate (*R*)-61 (entry 15, Table 1). The title compound was obtained in 73% isolated yield as pale yellow oil after purification on silica using isocratic mixture of heptane/EtOAc (85/15, v/v). ^{1}H NMR ($CDCl_3$) δ 7.78−7.81 (m, 2H), 7.35−7.40 (m, 2H), 7.22−7.27 (m, 2H), 6.08 (q, J = 6.6 Hz, 1H), 5.53 (d, J = 10.9 Hz, 1H), 5.24 (d, J = 10.9 Hz, 1H), 3.51−3.57 (m, 2H), 2.08 (s, 3H), 1.77 (d, J = 6.6 Hz, 3H), 0.91−0.95 (m, 2H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.4, 146.8, 140.8, 133.8, 128.5, 126.9, 125.0, 116.0, 75.2, 66.4, 63.9, 21.2, 19.2, 17.8, −1.4. HRMS calcd for $C_{19}H_{29}N_2O_3Si$ (M^+ + 1) 361.1947, found 361. $[\alpha]^{rt}_D$ (2.8 mg/mL, $CHCl_3$) +71.1

Synthesis of (1*S*)-1-[3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl]ethanol (*S*)-13 (Scheme 3). L-(+)-Lactic acid (2.83 g, 31.5 mmol), **12** (6.15 g, 28.6 mmol), and 1-hydroxybenzotriazole (386 mg, 2.86 mmol) was dissolved in DMSO (30 mL). While stirring at ambient temperature, *N*,*N*'-dicyclohexylcarbodiimide (4.69 g, 37.2 mmol) was added dropwise. After stirring for 4 h,

another portion of L-(+)-lactic acid (773 mg, 8.6 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (3.6 g, 28.6 mmol) was added, and the mixture was stirred for additional 3 h. Ethanol (200 mL) was added, and the mixture was refluxed for 4 h. The ethanol was removed by concentration *in vacuo*, and the resulting residue taken up in water (400 mL). The aqueous solution was extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The obtained crude product was purified by silica gel flash chromatography (*n*-hexane/ethyl acetate 100:0 to 80:20) to yield analytically pure title compound as a white solid (3.81 g, 50%) from the first eluting product containing fractions. The fractions eluting right thereafter contained less pure product, which was obtained as a waxy solid (2.72 g, 35%). ^{1}H NMR (DMSO-d_6) δ 7.94 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 6.19 (d, J = 5.8 Hz, 1H), 5.06 (m, 1H), 1.54 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 182.3, 166.8, 132.4, 129.0, 125.4, 125.2, 61.5, 21.3. HRMS calcd for $C_{10}H_{10}BrN_2O_2$ ($M^+ + 1$) 268.9926, found 268.9944. $[\alpha]^{rt}_D$ (2.6 mg/mL, $CHCl_3$) −3.8.

Preparation of (1*S*)-1-[5-(4-Bromophenyl)-1,2,4-oxadiazol-3-yl]ethanol (*S*)-9 and (1*R*)-1-[5-(4-Bromophenyl)-1,2,4-oxadiazol-3-yl]ethyl Acetate (*R*)-10 by KR of (*rac*)-1-[5-(4-Bromophenyl)-1,2,4-oxadiazol-3-yl]ethanol (*rac*)-9. Isopropenyl acetate (3.60 g, 35.7 mmol), (*rac*)-**9** (3.20 g, 11.89 mmol), and N435 (500 mg) were stirred in toluene (200 mL) for 72 h at ambient temperature. The mixture was then filtered and concentrated *in vacuo* to give a crude product, which was separated by silica gel flash chromatography (gradient from *n*-hexane to *n*-hexane/ethyl acetate 6:4). (*R*)-**10** eluted as the first material and was obtained as a yellowish oil (1.81 g, 49%), followed by (*S*)-**9** that was obtained as a white solid (1.58 g, 49%). (*R*)-**10**: ^{1}H NMR (DMSO-d_6) δ 8.04 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 5.98 (q, J = 6.6 Hz, 1H), 2.10 (s, 3H), 1.61 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 174.8, 170.4, 169.5, 132.7, 129.8, 127.4, 122.3, 63.8, 20.6, 18.5; Anal. Calcd for $C_{12}H_{11}BrN_2O_3$: C, 46.3; H, 3.6; N, 9.0. Found: C, 46.4; H, 3.7; N, 9.3. $[\alpha]^{rt}_D$ (2.5 mg/mL, $CHCl_3$): +101.1. (*S*)-**9**: The ^{1}H NMR spectrum was identical to that obtained for (*rac*)-**9**. Anal. Calcd for $C_{10}H_9BrN_2O_2$: C, 44.6; H, 3.4; N, 10.4. Found: C, 44.5; H, 3.5; N, 10.3. $[\alpha]^{rt}_D$ (2.6 mg/mL, $CHCl_3$) −123.1.

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Supporting Information Available: Synthesis and analysis data for all substrates, (D)KR experimental conditions, as well as Cartesian coordinates of calculated complexes. This material is available free of charge via the Internet at http://pubs.acs.org.