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Asymmetric Synthesis of Multi-Substituted Tetrahydrofurans via Palladium/Rhodium Synergistic Catalyzed [3+2] Decarboxylative Cycloaddition of Vinylethylene Carbonates

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Abstract: Unlike the comprehensive development of tandem multi-metallic catalysis, bimetallic synergistic catalysis has been challenging to achieve high stereoselectivity with the generation of multi-stereogenic centers. Herein, an efficient synergistic catalysis for the diastereo- and enantioselective synthesis of multi-substituted tetrahydrofuran derivatives has been developed. Under mild reaction conditions, a series of target molecules with three consecutive stereocenters were synthesized by a palladium(0)/rhodium(III) bimetal-catalyzed asymmetric decarboxylative [3+2]-cycloaddition of vinylethylene carbonates with α,β-unsaturated carbonyl compounds. The corresponding adducts were obtained with moderate to high yields (67%~98%) and excellent stereoselectivities (>20:1 d.r., up to 99% ee).

A simple access via asymmetric catalysis to construct multiple stereogenic centers in one step is a persistent challenge in synthetic chemistry, especially the formation of tertiary carbon and quaternary carbon chiral centers in cyclization reaction that requires overcoming ring strain and steric hindrance. Multi-substituted tetrahydrofuran scaffolds widely exist in many natural products and synthetic drugs, for example, natural nucleosides Guanosine hydrate[1] and Adenosine, anti-*Mycobacterium tuberculosis* agent Streptomycin,[2] antitumor agent Mucocin[3] and antibiotic feed additive Lasalocid[4] (Figure 1). At present these compounds were commonly generated from carbohydrate derivatives bearing a multiple hydroxyl

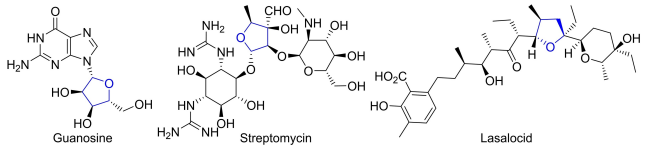
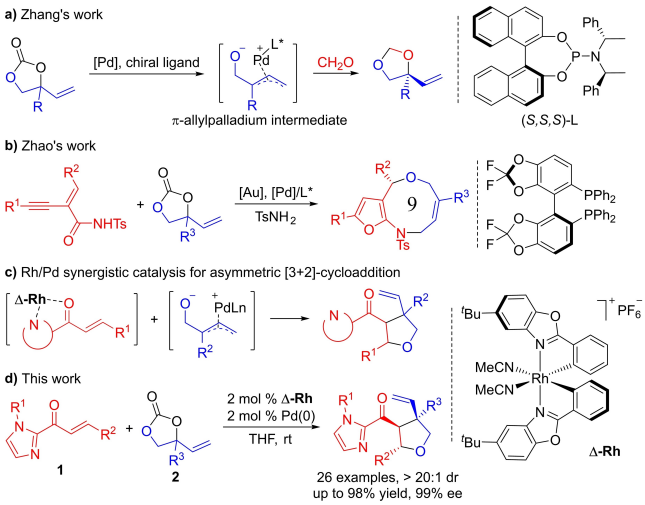


Figure 1. Representative examples of natural products with the framework of multi-substituted tetrahydrofuran.

structure,[1,3] epoxide-opening cyclization cascade,[4,5] intramolecular cycloaddition of alcohols,[6] Lewis acid catalyzed Prins reaction,[7] carbene O–H insertion[8] and so on. Considering the complex structure and distinct biological activity, and also the potential clinical application, a highly efficient catalytic pathway to expand the structural diversity of multi-substituted tetrahydrofuran derivatives is still in high demand.

In 2014, Zhang and co-workers[9a] reported first time the asymmetric decarboxylative cycloaddition of racemic vinylethylene carbonates (VECs) and formaldehyde catalyzed by palladium using phosphoramidite as ligand, delivering the five-membered ring 1,3-dioxolanes as methylene acetal protected tertiary vinylglycols (Scheme 1a). Recently, Zhao[9i] has developed an enantioselective gold/palladium sequential catalytic system that produce furan-fused nine-membered heterocycles



Scheme 1. Transition metal catalysis for asymmetric transformations from vinylethylene carbonates (VECs).

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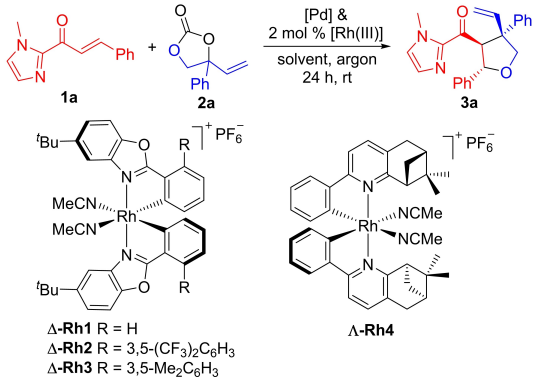
from enynamides and VECs (Scheme 1b). Researches suggested that VECs could undergo decarboxylation to afford a nucleophilic 1,3-dipolar π-allylpalladium intermediate[9] (Scheme 1a), which later developed into a typical method for synthesis of chiral multi-substituted tetrahydrofuran derivatives.[10] Inspired by our previous works in developing the catalytic [3+2]-cycloaddition between 1,3-dipoles and chiral Lewis acid activated dipolarophiles,[11] it would be logical to expect that the zwitterionic π-allylpalladium intermediate would react with unsaturated electrophiles under catalysis of chiral-at-metal rhodium(III) complexes[12] via a stereocontrolled addition and ring-closing reaction to afford the desired multi-substituted tetrahydrofuran (Scheme 1c).

Much progress has been made in one-pot multimetallic catalysis,[13] which not only behaves economic and environmental benefits but also enables some complex transformations that would be difficult to access by conventional methods. However, fewer examples of asymmetric syntheses via synergistic multi-metallic catalysis have been realized,[14] not to mention the construction of multiple stereogenic centers in one-pot in such catalytic system. Transition metal catalysis is highly dependent on ligands to confer specific reactivity, especially chiral ligands for asymmetric catalysis. However, in a multi-metal catalyzed system, competitive coordination and activation between each metal, ligand and substrate is always a crucial problem influencing reaction success. But the characteristic of the chiral-at-metal complex was somewhat different, the central metal binds with ligands through stable covalent bonds, and the complex would mediate the catalytic cycle without major ligands exchanged or released.[15] Thus, we envisioned that the chiral-at-metal complex would be more suitable for asymmetric multimetallic catalysis to work with other metal cooperatively.[11c,16] Herein, a highly efficient palladium-rhodium-catalyzed asymmetric decarboxylative [3+2]-cycloaddition of α,β-unsaturated 2-acyl imidazoles **1** with VECs **2** was reported (Scheme 1d). A novel approach for synthesizing chiral 1,2,3,3-tetrasubstituted tetrahydrofurans has been developed from racemic raw compounds in high level of stereoselectivities and yields.

The research was commenced by testing the model substrates α,β-unsaturated 2-acyl imidazole **1a** and racemic phenyl-VEC **2a**. In the presence of 2 mol% **Δ-Rh1**[15] and 1 mol% $Pd(PPh_3)_4$, after 24-hours reaction under argon atmosphere in DCM at room temperature, the desired product **3a** was obtained in 81% yield with 90% ee and >20:1 d.r. (Table 1, entry 1). The encouraging result supports our hypothesis that the chiral-at-metal complex fits for such bimetallic catalytic system. Chiral rhodium complexes **Δ-Rh2**, **Δ-Rh3**[17] and **Λ-Rh4**[16] were synthesized and examined, but yields and stereoselectivities were less than that derived from **Δ-Rh1** (entries 2–4). Without the rhodium complex, the reaction did not proceed at all (entry 5). Several Pd(0) and Pd(II) without chiral ligands were tested while the best option was $Pd_2(dba)_3{\cdot}CHCl_3$ (entries 6–9). A control experiment shows Pd(II) gave no reaction (entry 8). Besides, a series of anhydrous aprotic solvents were examined (entries 10–12). THF could give the best reactivity performance to reach 96% ee as there is a little increase in the yield and enantioselective (entry 10). Notably, an increment of the yield was detected by increasing the equivalent of $Pd_2(dba)_3{\cdot}CHCl_3$ to 2 mol%, delivering the target molecular in 88% yield together with 98% ee (entry 13). In all cases, a >20:1 d.r. value was obtained.

Table 1. Optimization of reaction conditions.[a]



Δ-Rh1 R = H
Δ-Rh2 R = 3,5-$(CF_3)_2C_6H_3$
Δ-Rh3 R = 3,5-$Me_2C_6H_3$

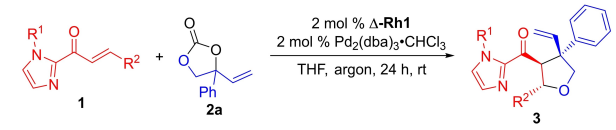
Λ-Rh4

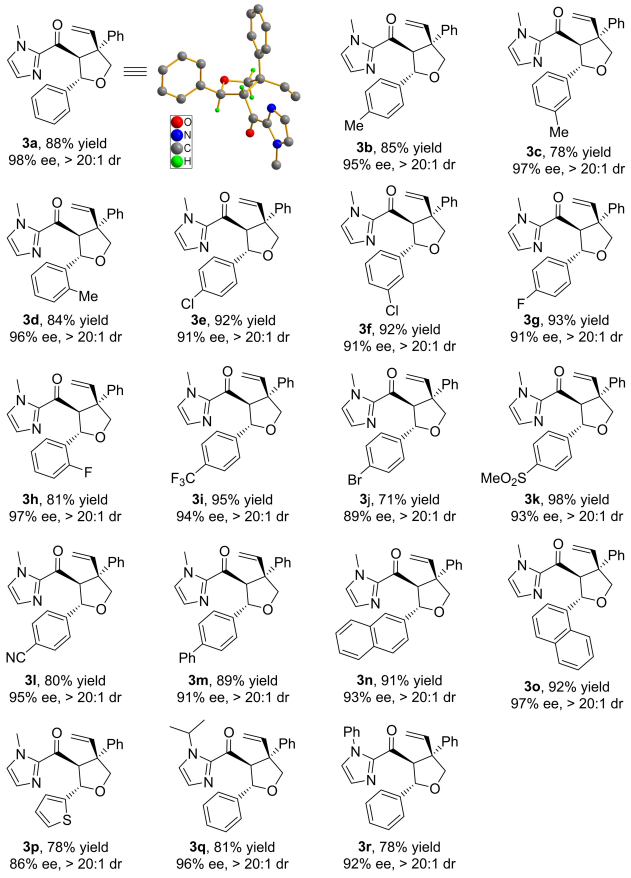
Entry	Rh	Pd (mol %)	Solvent	Yield (%)[b]	ee (%)[c] d.r.[d]
1	**Δ-Rh1**	$Pd(PPh_3)_4$ (1)	DCM	81	90, >20:1
2	**Δ-Rh2**	$Pd(PPh_3)_4$ (1)	DCM	79	83, >20:1
3	**Δ-Rh3**	$Pd(PPh_3)_4$ (1)	DCM	75	86, >20:1
4	**Λ-Rh4**	$Pd(PPh_3)_4$ (1)	DCM	68	61, >20:1
5	none	$Pd(PPh_3)_4$ (1)	DCM	n.a.	–
6	**Δ-Rh1**	$Pd_2(dba)_3{\cdot}CHCl_3$ (1)	DCM	82	94, >20:1
7	**Δ-Rh1**	$Pd_2(dba)_3$ (1)	DCM	75	94, >20:1
8	**Δ-Rh1**	$Pd(OAc)_2$ (1)	DCM	n.a.	–
9	**Δ-Rh1**	none	DCM	n.a.	–
10	**Δ-Rh1**	$Pd_2(dba)_3{\cdot}CHCl_3$ (1)	THF	83	96, >20:1
11	**Δ-Rh1**	$Pd_2(dba)_3{\cdot}CHCl_3$ (1)	toluene	80	95, >20:1
12	**Δ-Rh1**	$Pd_2(dba)_3{\cdot}CHCl_3$ (1)	1,4-dioxane	n.a.	–
13	**Δ-Rh1**	$Pd_2(dba)_3{\cdot}CHCl_3$ (2)	THF	88	98, >20:1

[a] Unless otherwise noted, reactions were carried out by using **1a** (0.2 mmol), **2a** (0.22 mmol), Rh-complex (0.004 mmol, 2 mol%) and Pd-catalyst (0.002 mmol, 1 mol%) in anhydrous solvent (1 mL) at room temperature under argon atmosphere for 24 h. [b] Isolated yields of diastereomeric mixtures. [c] Enantiomeric excess of the major isomer, determined by chiral HPLC analysis. [d] Diastereomeric ratio, determined via ^1H NMR analysis of diastereomeric mixtures. n.a. = not available.

With the optimal reaction conditions, the generality of this protocol was first evaluated with different α,β-unsaturated 2-acyl imidazoles **1**, a wild range of substrates with different electronic and steric properties were tolerated under the standard conditions (Table 2). Significantly, excellent diastereoselectivities were obtained with more than 20:1 d.r. from reactions between various substrates **1** and phenyl-VEC **2a**. Absolute configuration of the product **3a** was determined by single-crystal X-ray diffraction.[18] In some cases the steric

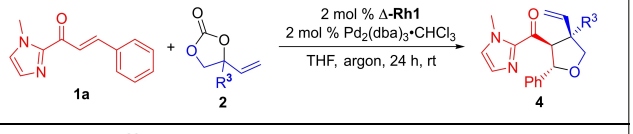
Table 2. Substrate scope of α,β-unsaturated 2-acyl imidazoles.[a]

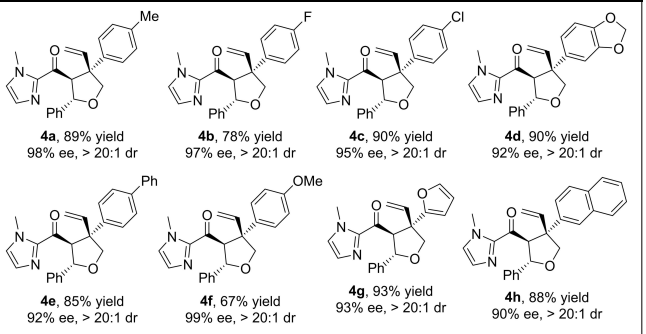




[a] Reaction conditions: reactions were carried out by using **1** (0.2 mmol), **2a** (0.22 mmol), **Δ-Rh1** (0.004 mmol, 2 mol%) and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 mmol, 2 mol%) in anhydrous THF (1 mL) at room temperature under argon atmosphere for 24 h. Yields were isolated yields. Ee values were determined by chiral HPLC analysis. The d.r. values were determined by ^{1}H NMR

Table 3. Substrate scope of vinylethylene carbonates.[a]





[a] Reaction conditions: reactions were carried out by using **1a** (0.2 mmol), **2** (0.22 mmol), **Δ-Rh1** (0.004 mmol, 2 mol%) and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 mmol, 2 mol%) in anhydrous THF (1 mL) at room temperature under argon atmosphere for 24 h. Yields were isolated yields. Ee values were determined by chiral HPLC analysis. The d.r. values were determined by ^{1}H NMR.

hindrance shows beneficial effect on enantioselectivity while no significant difference in yield (**3g**&**3h**, **3n**&**3o**), which is common in chiral-at-metal complexes catalyzed asymmetric reactions. β-Aryl substituents bearing electron-donating or -withdrawing groups were evaluated, no significant difference on reactivity and enantioselectivity was observed. Although Pd(0) might easily insert C-halogen bond, the 4-Br-phenyl substrate **1j** afforded good yield and enantiomeric excess (**3j**). However, 4-iodine-phenyl substrate had been tried without the goal product obtained.[19] β-Thienyl substrate **1p** was suitable, leading to the formation of the target molecule in high yield and enantiomeric excess (**3p**). However, β-furyl substrate was evaluated with very low yield (< 5%).[19] A possible reason was the relatively stronger electron-donating property of furyl increased the electron density on conjugated olefin, thus reduced its electrophilicity. Besides, *N*-isopropyl and *N*-phenyl substrates worked well, providing products **3q** and **3r** with good yields and excellent enantioselectivities. β-Alkyl and β-ethyl formate substituted substrates were tested, unfortunately, no title reaction was observed.[19] The mismatching of electronic property was supposed to be the major reason.

Further investigation of the substrate scope of VECs **2** was performed in catalyzed cycloaddition under optimal conditions with model substrate **1a** (Table 3). To our delight, good yields and excellent stereoselectivities were obtained among these substrates. Various VECs **2** bearing different aryl substituents were tolerated, even furyl substrate, delivering the target molecules in moderate to high yields and excellent stereoselectivities. However, when aromatic groups replaced with alkyl substituent (e.g., methyl-**2i**), the yield decreased to around 10% together with only 1.3:1 d.r..[19] The reaction involving this methyl-VEC substrate is the only one with poor d.r. value we tested. Compared with phenyl, methyl was short of aromatic π-electrons, which could stabilize the conjugated, positively charged π-allylpalladium in general. Also, the plausible reason for poor diastereoselectivity might be the steric hindrance, the full discussion will be shown in the mechanism section (Figure 2).

To demonstrate the synthetic utility of the current protocol, a gram-scale reaction was conducted. In the presence of 0.5 mol% of **Δ-Rh1** and 1 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, the decarboxylative cycloaddition of **1a** (848 mg, 4 mmol) and **2a** (836 mg, 4.4 mmol) at 40 °C for 32 h could generate the desired product **3a** in a diminished yield (1.15 g, 80%), with 96% ee and > 20:1 d.r. (Scheme 2a, 160 Rh-catalyst turnovers). Furthermore, the imidazole moiety of **3a** could be easily transferred to other functional groups.[20] For example, the two-steps transformation employing crystallized **3a** could afford aldehyde **5** in 71% yield

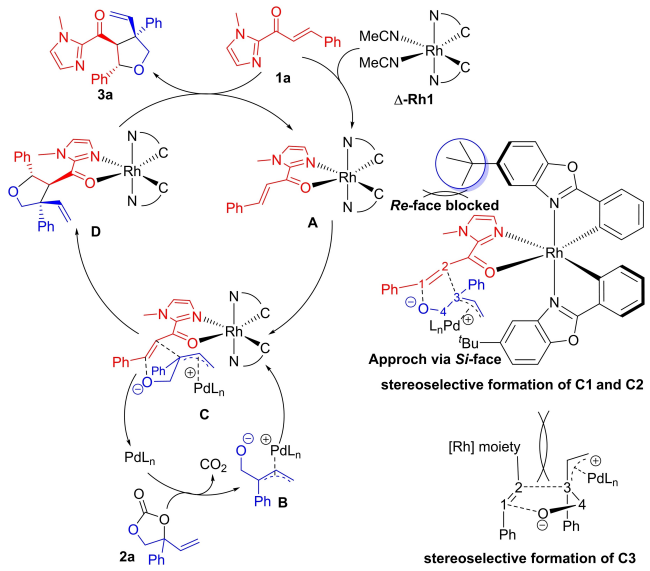
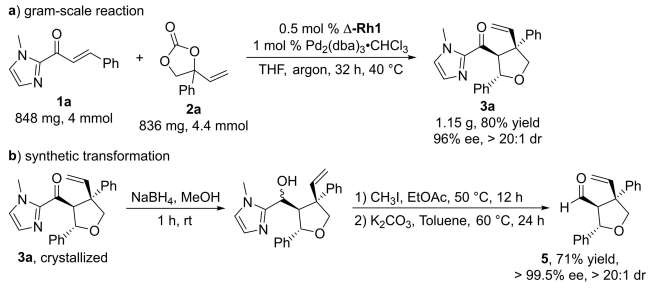


Figure 2. Plausible mechanism and transition state model.



Scheme 2. Gram-scale experiment and synthetic transformation.

(Scheme 2b) without any loss in enantiomeric excess (>99.5% ee, >20:1d.r.).

On the basis of the experimental results and literature precedents,[9,10,15] a plausible mechanism for the reaction is proposed (Figure 2). α,β-Unsaturated 2-acyl imidazole **1a** is activated by the chiral rhodium complex **Δ-Rh1** through bidentate *N,O*-coordination to form intermedia **A**. Meanwhile, phenyl-VEC **2a** undergoes palladium-catalyzed decarboxylative ring-opening process to generate a zwitterionic π-allylpalladium intermediate **B**. The *Re*-face of the α,β-unsaturated bond is shielded by one of the *tert*-butyl groups. The intermediate **B** can only approach the double bond via its *Si*-face. As a result, during the [3+2]-cycloaddition, the space configuration of C1, C2 is strictly determined. In addition, the steric repulsion between the aryl group of **2a** and Rh-coordinated 2-acyl imidazole group of **1a** leads to their opposite orientation on five-membered ring. The major isomer afforded by this intermedia fits the crystal analysis. During the evaluation of substrate scope of VECs, the poor diastereoselectivity caused by methyl-**2i**[19] might be due to the steric repulsion between the methyl group of **2i** and Rh-coordinated moiety of **1a** is not strong enough to make them orient oppositely. After the crucial formation of intermediate **C**, upcoming transfer is achieved through coordination dissociation and electron neutralization to generate intermediate **D**, which could undergo a substitution by **1a** to release the target molecule **3a**, and a new catalytic cycle is initiated.

In summary, an efficient bimetallic synergistic catalysis for enantioselective decarboxylative [3+2]-cycloaddition to synthesize the chiral multi-substituted tetrahydrofuran in one step has been developed. With the combination of a chiral-at-metal rhodium(III) complex and a palladium(0) catalyst, a wide scope of substrates were confirmed to have good reactivity and high stereoselectivity, implementing the direct formation of three consecutive stereocenters including one all-carbon quaternary center. The synthetic utility of the present process was demonstrated by the asymmetric synthesis of biologically relevant agents. Remarkable industrial potential is revealed through a gram-scale experiment and synthetic transformation. Besides, a typical methyl-VEC substrate illustrates the plausible reason for high diastereoselectivity and inspires us to design optimal substrates together with novel metal-ligand catalysts for asymmetric synthesis.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · bimetallic catalysis · cycloaddition · multi-substituted tetrahydrofurans · synergistic catalysis

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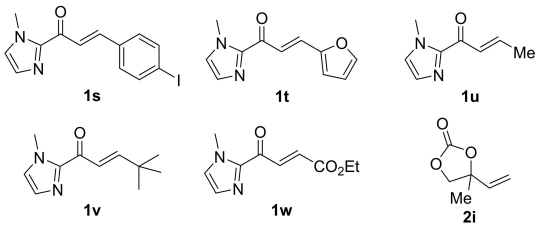
[18] Deposition Number 2054201 (for **3a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[19] Some substrates mentioned with poor reactivities were list:



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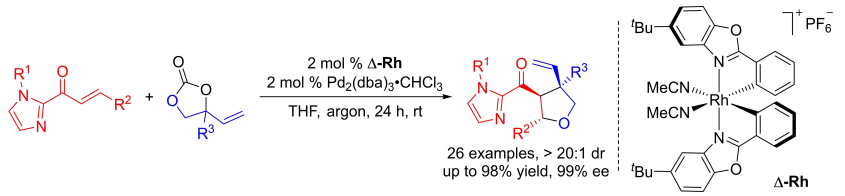

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Multimetallic cooperative catalysis represents one of the most efficient method for asymmetric C–C and C-heteroatom bond forming transformations. An enantioselective [3 + 2] cycloaddition reaction catalyzed synergistically by the combination of an achiral palladium catalyst and a chiral-at-metal rhodium(III) complex has been developed, generating a series of 1,2,3,3-tetrasubstituted tetrahydrofurans in high yields and stereoselectivities (> 20 : 1 d.r., up to 99 % ee).