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Asymmetric synthesis of 4-aryl-1,2,5-thiadiazolidin-3-one 1,1-dioxides *via* Pd-catalyzed hydrogenation of cyclic ketimines†

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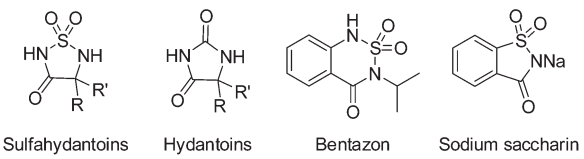
An efficient access to optically active sulfahydantoins, 4-aryl-1,2,5-thiadiazolidin-3-one 1,1-dioxides, was developed through palladium-catalyzed asymmetric hydrogenation of the corresponding cyclic *N*-sulfonylketimines with up to 98% ee.

Sulfahydantoins, 1,2,5-thiadiazolidin-3-one 1,1-dioxides, are valuable substructures with potential pharmacological properties and industrial utility.[1] They are the structural analogues of hydantoins, 2,4-imidazolidinediones, which are found in several medicinally important compounds and well known as anticonvulsant drugs for the management of epilepsy.[2] Notably, the heterocyclic ring in sulfahydantoins is a highly effective peptide-mimetic scaffold and their sulfone derivatives are found to be efficient inhibitors of serine proteinases.[3] What's more, sulfahydantoins are functionally related to herbicides (bentazon) and sweeteners (sodium saccharin) owing to their common sulfonamide functional group (Scheme 1).[4]

The diverse biological and chemical properties of sulfahydantoins have promoted the interest of organic chemists. Consequently, various synthetic methods have been developed for the construction of sulfahydantoins.[1,5] Noteworthily, some special biological properties are closely linked with the absolute configuration of compounds, but the preparation of optically pure sulfahydantoins has been explored scarcely. A general access to chiral sulfahydantoins was provided by Montero's group through alkaline cyclization starting from chiral *N*-sulfamylamino acid alkyl esters and a series of improvements have been made by other groups, but access to chiral *N*-sulfamylamino acid alkyl esters has strictly limited the application of this strategy (eqn (1), Scheme 2).[5] Recently, Nishimura's and Xu's groups separately documented the enantioselective synthesis of diaryl sulfahydantoins through Rh-catalyzed arylation of cyclic ketimines and moderate to high enantioselectivities could be obtained (eqn (2), Scheme 2).[6] To satisfy the increasing demand for diverse chiral sulfahydantoins, developing facile and efficient strategies is still highly desirable.



Scheme 1 Analogues of sulfahydantoins.

According to the retrosynthetic analysis of chiral 4-aryl sulfahydantoins, asymmetric hydrogenation of the corresponding cyclic *N*-sulfonylketimines is one of the most efficient and atom-economic approaches. In the search for an effective way to the asymmetric hydrogenation of imines, various catalytic systems such as organocatalysts and a number of transition-metal-based catalysts have made a great achievement.[7] Specially, over the last few decades, palladium has gradually grown up as an efficient and popular metal catalyst in asymmetric hydrogenation and much progress has been made,[7h] including functional olefins,[8] enamines,[9] ketones,[10] as well as aromatic compounds.[7f,11] Notably, the palladium catalyst has shown its powerful ability in the hydrogenation of activated imines.[12–14] Pioneering work by Amii and co-workers established the use of $Pd(OCOCF_3)_2$/BINAP as a catalyst for asymmetric hydrogenation of α-fluorinated imino esters with up to 91% ee.[12] In 2006, Zhang's group documented a palladium-catalyzed asymmetric hydrogenation of *N*-tosylimines with up to 99% ee.[13] Subsequently, using palladium catalytic systems, a series of cyclic sulfonamide and sulfamidate substrates have been successfully hydrogenated in Zhou's group with excellent yields and enantioselectivities.[14] Considering the similar *N*-sulfonylketimine structure and the practicability of palladium catalysts, we became interested in exploring the synthesis of chiral sulfahydantoins *via* a palladium-catalyzed

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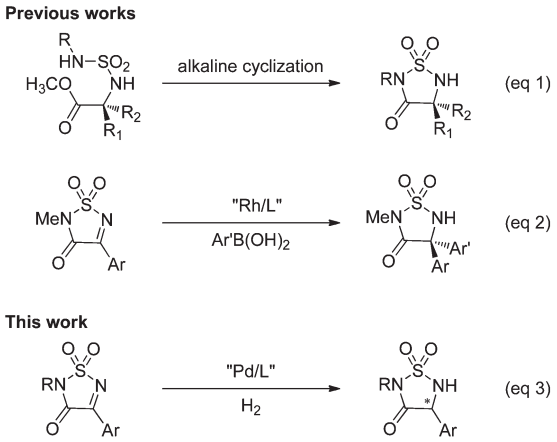
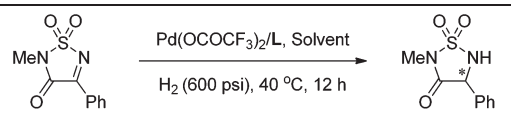


Scheme 2 Synthesis of chiral sulfahydantoins.

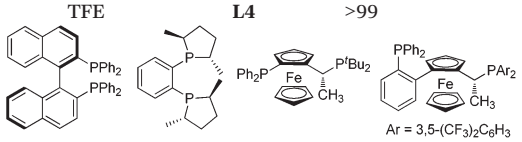
hydrogenation strategy. Herein, we present an efficient method for the enantioselective synthesis of 4-aryl sulfahydantoins by asymmetric hydrogenation of the corresponding cyclic ketimines using the chiral palladium complex as a catalyst, and up to 98% ee was obtained (eqn (3), Scheme 2).

At the outset, using cyclic *N*-sulfonylketimines **1a** as model substrates, the reaction conditions for the palladium-catalyzed asymmetric hydrogenation of **1a** were investigated. Initial examinations began with the solvents. The reaction proceeded smoothly in TFE (2,2,2-trifluoroethanol) with 89% yield and 16% ee (Table 1, entry 1). However, a racemic product was obtained when the reaction was conducted in methanol and poor reactivity was obtained in dichloromethane or toluene (Table 1, entries 2–4). To further improve the reaction efficiency, we investigated different chiral ligands' influence

Table 1 Evaluation of the reaction parameters[a]

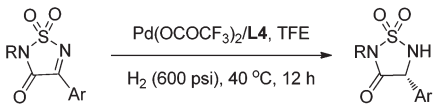


Entry	Solvent	L	Yield[b] (%)	ee[c] (%)
1	TFE	**L1**	89	16
2	CH_2Cl_2	**L1**	35	17
3	Toluene	**L1**	18	10
4	MeOH	**L1**	80	0
5	TFE	**L2**	84	36
6	TFE	**L3**	89	71
7	TFE	**L4**	>99	98



[a] Conditions: **1a** (0.1mmol), $Pd(OCOCF_3)_2$ (2.0 mol%), **L** (2.4 mol%), solvent (1.5 mL), H_2 (600 psi), 40 °C, 12 h. [b] Isolated yields. [c] Determined by HPLC.

Table 2 Asymmetric hydrogenation of cyclic *N*-sulfonylketimines **1**[a]



Entry	R	Ar	Yield[b] (%)	ee[c] (%)
1	Me	C_6H_5	>99 (**2a**)	98
2	Et	C_6H_5	98 (**2b**)	96
3	Bn	C_6H_5	94 (**2c**)	94
4[d]	Me	2-$CH_3C_6H_4$	99 (**2d**)	80
5	Me	3-$CH_3C_6H_4$	98 (**2e**)	98
6	Me	4-$CH_3C_6H_4$	>99 (**2f**)	97
7[d]	Me	4-$CH_3OC_6H_4$	98 (**2g**)	97
8[d]	Me	4-FC_6H_4	99 (**2h**)	97
9[d]	Me	4-ClC_6H_4	99 (**2i**)	96
10[d]	Me	4-BrC_6H_4	96 (**2j**)	94
11	Me	2-Naphthyl	95 (**2k**)	93

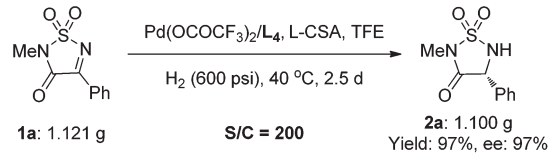
[a] Conditions: **1** (0.2 mmol), $Pd(OCOCF_3)_2$ (2.0 mol%), **L4** (2.4 mol%), TFE (3.0 mL), H_2 (600 psi), 40 °C, 12 h. [b] Isolated yields. [c] Determined by HPLC. [d] 10 mol% L-CSA (L-camphorsulfonic acid) was added.

on the reactivity and enantioselectivity. Fortunately, when we chose ferrocene-derived bisphosphine **L4** as a ligand, both excellent reactivity and 98% of enantioselectivity were obtained (Table 1, entry 7). Therefore, the optimal reaction conditions were established: $Pd(OCOCF_3)_2$/**L4** as the catalyst, TFE as the solvent and the reaction temperature was 40 °C.

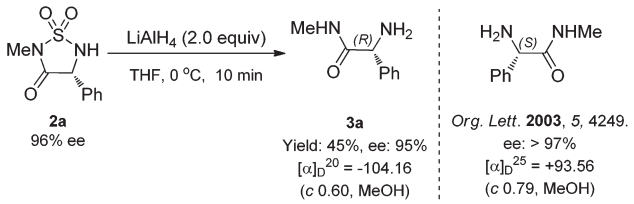
With the optimal reaction conditions in hand, a range of 4-aryl substituted cyclic *N*-sulfonylketimines **1** were investigated and the results are shown in Table 2. For different *N*-protected groups, the methyl group afforded the highest 98% ee value, which was better than that of the ethyl group or benzyl group (Table 2, entries 1–3). Notably, the steric effect of the aryl substituents of substrate **1** obviously influenced the reaction (Table 2, entries 4–6), when a methyl group was introduced to the *ortho*-position of the phenyl ring, the transformation displayed poor reactivity and moderate 80% ee of enantioselectivity. To improve the reactivity, acid additives were screened and when 10 mol% L-CSA was added without affecting the enantioselectivity, the reaction proceeded smoothly with 99% yield in 12 h (Table 2, entry 4). With the help of an acid additive, substrates with different electron-withdrawing groups such as fluorine, chlorine and bromine also proceeded smoothly, giving the desired products in high yields and ee values (Table 2, entries 8–10). In addition, the naphthyl group was also tolerated in the reaction (Table 2, entry 11).

Moreover, to further demonstrate the practicality of the above hydrogenation strategy, 0.5 mol% palladium catalyst was used in the hydrogenation of model substrate **1a** on a gram scale without any loss of reactivity and enantioselectivity, and the desired product was obtained in 97% yield and 97% ee (Scheme 3).

To determine the absolute configuration of the hydrogenation product, **2a** was transformed into the known compound



Scheme 3 Gram scale experiment.



Scheme 4 Determination of the absolute configuration of **2a**.

3a by a simple transformation of reduction with lithium aluminium hydride in THF (Scheme 4). Compared with the ^{1}H NMR, HPLC, and optical rotation data reported by a reference, the absolute configuration of **2a** was determined to be the *R* configuration.[15]

Conclusions

In summary, we have reported a highly efficient access to a series of optically active 4-aryl sulfahydantoin derivatives *via* palladium-catalyzed asymmetric hydrogenation of the corresponding cyclic *N*-sulfonylketimines with up to 98% ee. Further efforts to achieve the asymmetric hydrogenation of some other functionalized imines are ongoing in our laboratory.

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