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Transfer Hydrogenation of α-Branched Ketimines: Enantioselective Synthesis of Cycloalkylamines *via* Dynamic Kinetic Resolution

Abel Ros,[a] Antonio Magriz,[a] Hansjörg Dietrich,[b] Mark Ford,[b] Rosario Fernández,[c,*] José M. Lassaletta[a,*]

[a] Instituto de Investigaciones Químicas (CSIC-USe), Americo Vespuccio s/n, Isla de la Cartuja, 41092 Seville, Spain
Fax: (+34)-95-446-0565. e-mail: jmlassa@iiq.csic.es
[b] Bayer CropScience GmbH, Industriepark Höchst G386, 65926 Frankfurt am Main, Germany
[c] Dpto. de Química Orgánica, Universidad de Sevilla, Apdo. de Correos 553, 41071 Seville, Spain

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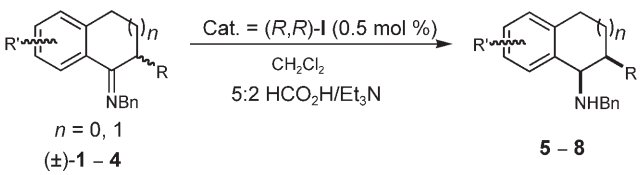
Abstract: The transfer hydrogenation of 2-substituted bicyclic and monocyclic ketimines using HCO_2H/Et_3N as the hydrogen source and TsDPEN-based Ru(II) and Ir(III) catalysts proceeds with dynamic kinetic resolution to afford the corresponding *cis*-cycloalkylamines with moderate to excellent levels of diastero- and enantioselectivity. A "one-pot" procedure starting from ketones as starting materials with *in situ* formation of the reacting imines has also been developed.

Keywords: amines; asymmetric catalysis; dynamic kinetic resolution; iridium; ruthenium; transfer hydrogenation

In spite of the enormous advances in asymmetric synthesis and catalysis during the last decade, the resolution of racemates remains as the most important approach used by the chemical industry for the preparation of enantiomerically pure or enriched compounds. In this context, dynamic kinetic resolution (DKR)[1] appears to be the most efficient option, overcoming the limitation of 50% maximum yield associated with conventional separation techniques or classical kinetic resolutions. A synthetically important group of transformations that can be combined with DKR techniques involves the transition metal-catalyzed asymmetric hydrogenation of a configurationally labile carbonyl compound. The seminal work by the groups of Noyori[2] and Genêt[3] on the hydrogenation of β-keto esters has stimulated a number of applications[1] and the development of related reactions such as the transfer hydrogenation of benzils[4] and of several types of 2-substituted cycloalkanones.[5]

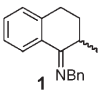
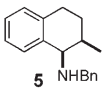
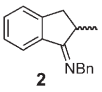
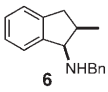
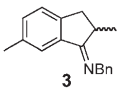
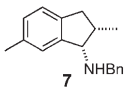
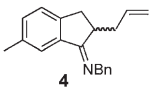
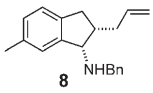
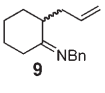
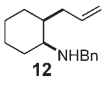
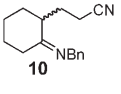
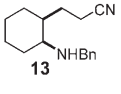
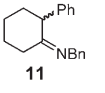
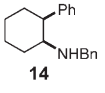
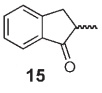
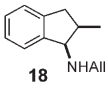
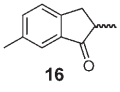
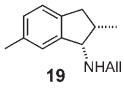
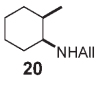
On the other hand, the efficiency of asymmetric transfer hydrogenation of imines by Ru(II)[6] and Rh(III)[7] catalysts has been demonstrated. Analyzing the above information globally, it can be foreseen that the combination of DKR techniques with the transfer hydrogenation of α-substituted racemic ketimines would appear as an attractive synthetic tool of high academic and industrial interest. The absence of reports on DKRs with reduction of an imine C=N bond is therefore highly surprising. In this communication, we report on the first examples of DKR involving these type of reactions.

Experiments were conducted in CH_2Cl_2 using the 5:2 HCO_2H-Et_3N azeotropic mixture as the hydrogen source, chosen taking into account the high reactivity of imines in this medium[6] and that a fast racemization *via* enamines is expected to occur. Initially, the readily available tetralone and indanone imine derivatives **1**–**4** were chosen as the racemic substrates (Scheme 1). Although reduction of the tetralone derivative (**1**) proceeded with complete *cis* selectivity for all the catalysts **I**–**III** tested (Figure 1), the enantioselectivity of the product **5** was only modest for Noyori's RuCl(*p*-cymene)TsDPEN catalyst **I** (Table 1, entry 1), while use of Ir(Rh)ClCp*TsDPEN catalysts **II** and **III** afforded **5** in higher 75–80% yields but negligible ees. In contrast, the indanone derivatives (**2**–**4**) in combination with **I** se-



Scheme 1. Dynamic kinetic resolution of bicyclic ketimines.

Table 1. Transfer hydrogenation of branched cyclic ketimines. Enantioselective synthesis of α-substituted cycloalkylamines *via* DKR.

Entry	Substrate	Solvent	Method[a]	Catalyst	S/C	*t* (d)	Product	Conf.	Yield[b]	*cis*:*trans*[c]	ee *cis* [%][d]
1	 **1**	CH_2Cl_2	**A**	(*R*,*R*)-**I**	200	5	 **5**	(*R*,*R*)	45	>99:1	50
2	 **2**	CH_2Cl_2	**A**	(*S*,*S*)-**I**	200	6	 **6**	(*R*,*R*)	70	>99:1	96
3	 **3**	CH_2Cl_2	**A**	(*S*,*S*)-**I**	200	6	 **7**	(*S*,*S*)	82	>99:1	97[e]
4	 **4**	CH_2Cl_2	**A**	(*R*,*R*)-**I**	200	5	 **8**	(*S*,*S*)	67	>99:1	92[e]
5	 **9**	CH_2Cl_2	**A**	(*S*,*S*)-**II**	500	1	 **12**	(*S*,*S*)	75 (70)[f]	93:7[g]	63[e]
6	 **10**	CH_2Cl_2	**A**	(*S*,*S*)-**II**	500	6	 **13**	(*S*,*S*)	60	96:4[h]	72[e]
7	 **11**	CH_2Cl_2	**A**	(*S*,*S*)-**II**	500	1	 **14**	(*S*,*S*)	55	>99:1	50[i]
8	 **15**	HCO_2H/Et_3N	**B**	(*R*,*R*)-**I**	200[j]	6	 **18**	(*R*,*R*)	55	>99:1	90[i]
9	 **16**	HCO_2H/Et_3N	**B**	(*S*,*S*)-**I**	200	6	 **19**	(*S*,*S*)	60	>99:1	>98[e]
10	 **17**	HCO_2H/Et_3N	**B**	(*S*,*S*)-**I**	200	8	 **20**	(*S*,*R*)	77	92:8	90[i]

[a] Method **A** uses preformed benzyl imines; method **B** uses ketones as starting materials with *in situ* condensation to the reacting imines.
[b] Isolated, overall yield from starting ketone.
[c] Determined by ^{1}H NMR of the crude reaction mixtures.
[d] Determined by HPLC on chiral stationary phases. See Supporting Information for details.
[e] Determined for the corresponding benzamide.
[f] In parenthesis, isolated yield of pure *cis* product.
[g] Separable mixture of *cis* and *trans* isomers.
[h] Pure *cis* product was obtained upon preparation and purification of the corresponding hydrochloride.
[i] Determined for the corresponding acetamide.
[j] On increasing the amount of (*R*,*R*)-**I** to S/C 100, **18** was obtained in similar 58% yield but lower 74% ee, while 1(*R*,*R*)-2-methylindan-1-ol was obtained as by-product in 20% yield.

lectively afforded the expected *cis* amines **6**–**8** in moderate-to-good yields and excellent ees (entries 2–4). Use of the Ir(III) complex **II** as the catalyst also afforded the *cis* product **6** selectively (*cis*:*trans* >99:1), but in a poorer 60% yield and a much lower 60% ee.

We next turned our attention to monocyclic substrates such as **9**–**11** (Scheme 2). These are *a priori* more challenging systems where the smaller steric and electronic differences at both sides of the carbonyl group and the *Z*/*E* isomerization of the imine C=N bond constitute additional difficulties. However, it was possible again to develop a synthetically useful reaction based on a DKR process: using Ir complex **II** as the catalyst of choice in this case, products **12**–**14** were isolated with high *cis* selectivities, moderate yields and remarkable ees for these systems (entries 5–7). Alternative use of catalysts **I** or **III** afforded products in lower yields and ees.

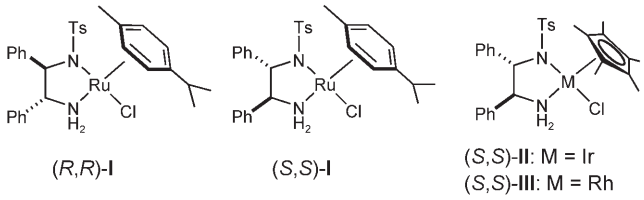


Figure 1. TsDPEN-based catalysts.

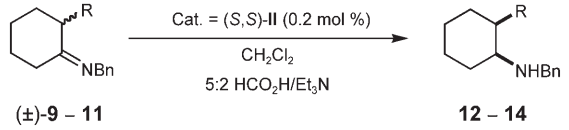
According to the early findings by Noyori,[6] imines react faster than ketones in transfer hydrogenation using HCO_2H/Et_3N as the hydrogen source and type-**I** Ru(II) catalysts. Therefore, we decided to explore the selective "one-pot" transfer hydrogenation of *in situ* generated allyl imines (Scheme 3). Thus, ketones **15**–**17**, representatives of both types of substrates, were used directly as starting materials in "solvent-free" reactions[8] carried out in the presence of an excess of allylamine. The results collected using this technique (entries 8–10) confirmed the expected C=N/C=O chemoselectivity: *cis* allylamines **18**–**20** were obtained with similar overall yields and selectivities as from preformed benzylimines. This method provides a more convenient procedure for the operational simplicity, in particular when the synthesis of the alternative imine precursor is troublesome. It is in addition worth mentioning that only Ru(II) catalyst **I** gave good results under these conditions.

Summarizing, transfer hydrogenation of α-substituted cyclic ketimines *via* DKR can be accomplished by using Noyori's Ru(arene)TsDPEN complex **I**, as well as related Ir(III) and Rh(III)-based catalysts **II** and **III**, and HCO_2H/Et_3N as the hydrogen source. These reactions provide the first known examples of a DKR-based process involving reduction of C=N bonds. The observed yields and the achieved levels of diastero- and enantioselectivity of the products confer synthetic utility to the methodology. A more detailed study to determine the scope and limitations of this new synthetic tool is currently being performed in our laboratory.

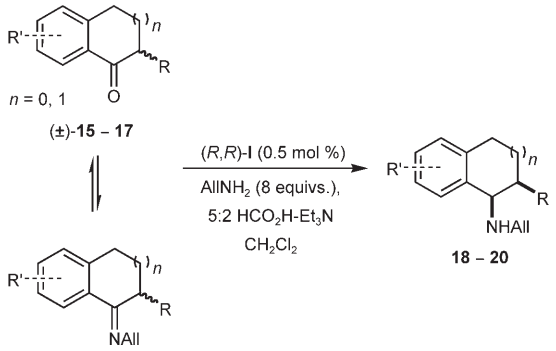
Experimental Section

Synthesis of Benzylketimines 1–4 and 9–11; General Procedure

A solution of the starting ketone (18 mmol), benzylamine (1.2 equivs., 2.36 mL) and *p*-toluenesulfonic acid (cat.) in dry toluene (60 mL) was heated to reflux overnight using a "Dean–Stark" system in order to remove water. The reaction mixture was concentrated and the crude product was used in the following step without further purification.



Scheme 2. Dynamic kinetic resolution of monocyclic ketimines.



Scheme 3. "One-pot" transfer hydrogenation to cycloalkylamines.

Transfer Hydrogenation of Ketimines

Method A: To a solution of catalyst **I**–**III** in a 5:2 HCO_2H/Et_3N azeotropic mixture (2.4 mL) was added a solution of the crude benzylimine **1**–**4** or **9**–**11** (5 mmol) in CH_2Cl_2 (7 mL). The mixture was stirred at room temperature for 1–6 days and the reaction was then diluted with CH_2Cl_2 (10 mL) and washed with a solution of Na_2CO_3 (0.5 M, 20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layer was dried and concentrated, and the residue was purified by flash chromatography.

Method B: A mixture of ketone **15**–**17** (4 mmol), allylamine (8 equivs., 2.4 mL) and anhydrous $MgSO_4$ (500 mg) was stirred at room temperature for 1 h. A solution of catalyst **I** (0.02 mmol, S/C = 200) in a 5:2 HCO_2H/Et_3N azeotropic mixture (2.4 mL) was then added and the mixture was stirred for 6 days. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and washed with a solution of Na_2CO_3 (0.5 M, 20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layer was dried ($MgSO_4$), concentrated and the residue was purified by flash chromatography.

Starting material, method used for the synthesis, catalyst, eluents, yields and spectral and analytical data for compounds **5**–**8**, **12**–**14**, and **18**–**20** are described in the Supporting Information.

Acknowledgements

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[8] Screening experiments revealed that addition of common solvents (CH_2Cl_2, CH_3CN, DMF, etc.) to the reaction mixture is detrimental to the C=N/C=O selectivity and the yield of the desired amine.
[9] The absolute configurations of (*R*,*R*)-**6** and (*S*,*S*)-**14** were assigned after chemical correlation with known compounds, while those of **5**, **7**, **8**, **12**, **13**, and **18–20** were assigned by analogy: a) Z. Zhang, G. Zhu, Q. Jiang, D. Xiao, X. Zhang, *J. Org. Chem.* **1999**, *64*, 1774–1775; b) T. Hayashi, T. Senda, M. Ogasawara, *J*, *Am. Chem. Soc.* **2000**, *122*, 10716–10717; see Supporting Information for details.

