Brønsted acid differentiated metal catalysis by kinetic discrimination†‡

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A Brønsted acid differentiated metal catalyzed hydrogenation has been developed. A combinatorial variation of chiral triflylamides with achiral metal complexes results in a highly active catalyst for the asymmetric reduction.

Over the past few decades, asymmetric catalysis has become a key feature of modern organic synthesis. Typically transition metal complexes bearing different chiral mono- or multidentate ligands were employed to perform reactions in a highly enantioselective fashion. Following the recent renaissance of organocatalysis numerous applications of metal-free reactions have additionally been reported.

The combination of organo- and transition metal catalysis is a contemporary concept and gives way to innovative reaction protocols that rely on the beneficial interplay of an organocatalyst and a metal catalyst.[1] The potential of combined Brønsted acid and metal catalysis has been demonstrated by initial applications.[2–4] However, in all the reactions developed only chiral phosphoric acid diesters or amino acids were utilized; the application of the more acidic *N*-triflylphosphoramides in combination with a metal catalyst has not been reported to date.

Given that achiral metal-triflimides and metal-triflates are highly reactive catalysts the analogous chiral metal–*N*-triflylphosphoramides should act as potent chiral catalysts for enantioselective transformations.

From a structural point of view, the anion of *N*-triflylphosphoramides can act similarly to the triflimide anion, either as a bidentate[5a] (Fig. 1a) or a monodentate ligand[5b,c] (Fig. 1b) or as a noncoordinating anion[5d,6] (Fig. 1c). Furthermore, protonation of the basic ligand by the chiral *N*-triflylphosphoramide may result in ion-pair formation in close proximity to the metal centre (Fig. 1d).[5e]

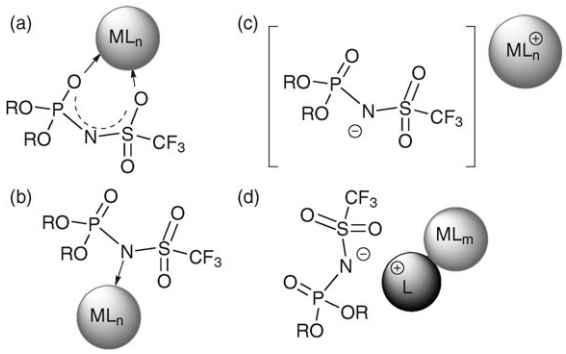


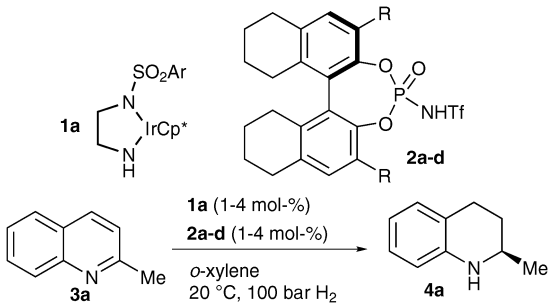
Fig. 1 Coordination properties of chiral *N*-triflylphosphoramides and a cationic metal complex.

We decided to examine the combination of an achiral iridium(III) diamine complex[7] and a chiral *N*-triflylphosphoramide. The Ir–diamine complexes are inactive in hydrogenation reactions; however, upon protonation by a strong Brønsted acid, they turn into highly active hydrogenation catalysts. If a chiral, strongly acidic Brønsted acid is applied, the acid not only activates the catalyst but also renders it chiral. Thus, enantioselectivities should be dependent on the chiral activating acid.

We started our investigations using an achiral ethylenediamine derived iridium(III) complex, different chiral *N*-triflylphosphoramides and quinaldine as a model substrate.[8] To our delight, selectivities strongly depended on the nature of the substituents in the 3,3′ position of the chiral *N*-triflylphosphoramide, demonstrating that the chiral Brønsted acid fulfils both before mentioned purposes.

The validity of this assumption is further underlined by the interesting observation that the absolute configuration of the reaction product depends on the substituents in the 3,3′ position of the chiral *N*-triflylphosphoramide (Table 1, entries 3 and 4). To further improve the selectivities of the reaction we decided to vary the ethylenediamine backbone. Thus, the selectivities and reactivities of the hydrogenation of quinaldine were efficiently increased (Table 2). Further reaction optimization included the evaluation of different sulfonylated DPEN

Table 1 Evaluation of different chiral Brønsted acids



Entry[a]	Mol%	R	HA	Time	Conv.[b]	e.r.[b]
1	4	Phenyl	**2a**	24	25	*rac*
2	4	4-*t*Bu-Phenyl	**2b**	24	25	43 : 57
3	4	TRIP	**2c**	24	50	31 : 69
4	1	9-Phenanthryl	**2d**	60	40	66 : 34

1: Ar = 2-Naphthyl, TRIP = 2,4,6-(^{i}Pr$_3$)Phenyl.[a] Reaction conditions: 0.15 mmol **3a**, 0.8 mL *o*-xylene, 1 mol% [Ir], 1 mol% additive. [b] Determined by GC on chiral stationary column.

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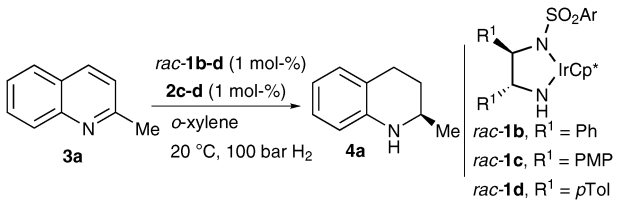
Table 2 Evaluation of different iridium(III) complexes



Entry[a]	R^1	R	HA	Time	Conv.[b]	e.r.[b]
1	Ph	TRIP	**2c**	14	80	58 : 42
2	Ph	9-Phenanthryl	**2d**	24	>95	91 : 9
3	PMP	9-Phenanthryl	**2d**	24	80	87 : 13
4	*p*-Tol	9-Phenanthryl	**2d**	24	>95	86 : 14

1: Ar = 2-Naphthyl, TRIP = 2,4,6-(^{i}Pr$_3$)Phenyl. [a] Reaction conditions: 0.15 mmol **3a**, 0.8 mL *o*-xylene, 1 mol% [Ir], 1 mol% additive. [b] Determined by GC on chiral stationary column.

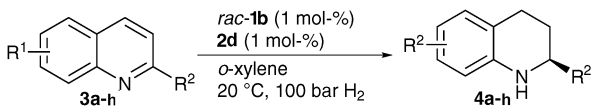
ligands and Brønsted acids. Moreover, the variation of solvents and hydrogen pressure was investigated.

These experiments showed that elevated hydrogen pressures and apolar, aromatic solvents are optimal for obtaining high selectivities. The latter finding supports the fact that non-protic solvents are beneficial in chiral ion-pair catalysis.

With the optimal conditions in hand, we examined the substrate scope of this newly developed asymmetric hydrogenation (Table 3). In general, a variety of 2′-substituted quinolines can be reduced to the corresponding tetrahydroquinolines in good yields and with good enantioselectivities if a racemic iridium(III) complex is used in combination with the chiral *N*-triflylphosphoramide **2d**.

With regard to the reaction mechanism we were interested in explaining the observed selectivities. Therefore, we prepared the enantiopure iridium(III) complexes (*R,R*)-**1b** and (*S,S*)-**1b** and tested both in combination with **2d** in the hydrogenation reaction of 2-methylquinoline. Interestingly it was observed that the two complexes were remarkably different with regard to both reactivity and selectivity. The combination including (*S,S*)-**1b** was less reactive than *rac*-**1b**. The opposite enantiomer (*R,R*)-**1b** exhibited slightly increased selectivities and further improvement was observed on cooling the reaction mixture. However, it is important to note that in order to perform this

Table 3 Substrate scope using the racemic iridium diamine complex



Entry[a]		R^1	R^2	Yield[b]	e.r.[c]
1	**4a**	H	Me	96	91 : 9
2	**4b**	6-F	Me	92	87 : 13
3	**4c**	6-Cl	Me	93	86 : 14
4	**4d**	6-Br	Me	97	84 : 16
5[d]	**4e**	8-Cl	Me	90	85 : 15
6[d]	**4g**	H	*n*-Butyl	99	85 : 15
7[d]	**4h**	H	*n*-Pentyl	95	83 : 17

[a] Reaction conditions: 0.3 mmol **3a–h**, 1.6 mL *o*-xylene, 1 mol% catalyst. [b] Yield of isolated product. [c] Determined by GC on chiral stationary column. [d] 2 mol% **1b**, 2 mol% **2d**.

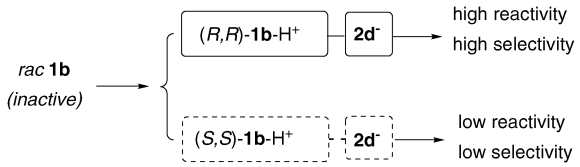


Fig. 2 Chiral Brønsted acid differentiated metal catalysis.

reaction in a highly enantioselective fashion chiral acidic additives are required as treatment of (*R,R*)-**1b** with the achiral *N*-triflylphosphoramide (TPA) leads to diminished selectivity.

Thus, the asymmetric induction of complex *rac*-**1b/2d** can only be rationalized by a kinetic differentiation of the two enantiomeric iridium catalysts.

Rac-**1b** is protonated by the chiral acid **2d**, resulting in two different complexes of which the combination (*R,R*)-**1b**–H^+/**2d**$^-$ is much more reactive than the combination of (*S,S*)-**1b**–H^+/**2d**$^-$. However, these diastereomeric complexes not only differ in their catalytic reactivity but also in the intrinsic selectivity (Fig. 2; Table 4, entries 3 and 5).[9,10]

Finally, we examined the substrate scope of the Brønsted acid differentiated iridium catalyzed hydrogenation of quinolines (Table 5). In general, a variety of different 2′-substituted quinolines, as well as different quinoline cores, can be reduced in good yields and with excellent enantioselectivities (up to 94% ee).

In summary, we herein report the first Brønsted acid differentiated metal catalyzed hydrogenation by kinetic discrimination. Applying this concept, we were able to show for the first time, that skillful combination of chiral *N*-triflylphosphoramides and cheap, racemic iridium complexes can be used to obtain good enantioselectivities. Furthermore, the optimal catalyst combination can be readily determined by utilizing a fast combinatorial approach in which racemic metal complexes are simply combined with chiral acids in order to identify the ideal catalyst system. To date, only chiral phosphoric acid diesters have been utilized in combination with metal complexes. Based on the different coordination properties of *N*-triflylphosphoramides (see Fig. 1) the repertoire of combined Brønsted acid–metal catalysis is not only enhanced by an additional Brønsted acid, but also by the possibility of designing substantially different chiral complexes bearing mono- or bidentate or even non-coordinating chiral anions that could conceivably exhibit distinct activation modes.

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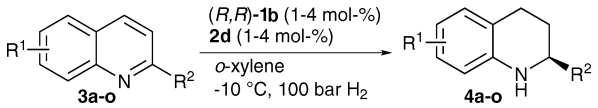
Table 4 Evaluation of the absolute configuration of the diamine complex

Entry[a]	**1b**	HA	Mol%	*T*/°C	Time/h	Conv.[b]	e.r.[b]
1	(*S,S*)-**1b**	—	1	20	24	no rct	—
2	(*R,R*)-**1b**	TPA	1	20	24	>95	72 : 28
3	(*S,S*)-**1b**	**2d**	1	20	40	75	16 : 84
4	*rac*-**1b**	**2d**	1	20	24	>95	91 : 9
5	(*R,R*)-**1b**	**2d**	1	20	24	>95	94 : 6
6	(*R,R*)-**1b**	**2d**	2	−10	36	>95	97 : 3

[a] Reaction conditions: 0.15 mmol **3a**, 0.8 mL *o*-xylene. [b] Determined by GC on chiral stationary column. TPA = $(PhO)_2P(O)NHTf$.

Table 5 Substrate scope of the Brønsted acid differentiated iridium catalyzed hydrogenation



Entry[a]	T/°C		R_1	R_2	Yield[b]	e.r.[c]
1	−10	**4a**	H	Me	92	97 : 3
2	−10	**4b**	6-F	Me	85	94 : 6
3	20	**4c**	6-Cl	Me	96	93 : 7
4	20	**4d**	6-Br	Me	98	92 : 8
5	20	**4e**	8-Cl	Me	83	92 : 8
6	−10	**4f**	H	*n*-Propyl	77	95 : 5
7	−10	**4g**	H	*n*-Butyl	82	94 : 6
8	−10	**4h**	H	*n*-Pentyl	84	95 : 5
9	−10	**4i**	H	*i*-Butyl	71	94 : 6
10	−10	**4j**	H	$-(CH_2)_2$–Ph	74	95.5 : 4.5
11	−10	**4k**	H	$-(CH_2)_2$–(3,4-$(OMe)_2$–Ph)	66	95 : 5
12	−10	**4l**	H	$-(CH_2)_2$–(3,4-OCH_2O–Ph)	72	96 : 4
13	−10	**4m**	H	$-(CH_2)_2$–(3-OMe–Ph)	81	96 : 4
14	−10	**4n**	H	$-(CH_2)_2$–(4-(Me)–Ph)	76	96 : 4

[a] Reaction conditions: 0.2 mmol **3a–n**, 1.0 mL *o*-xylene, 1–4 mol% **1b** and **2d**, reaction time 24–48 h, reaction temperature as indicated, 100 bar H_2 pressure. [b] Yield of isolated product. [c] Determined by GC or HPLC on chiral stationary column.

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