Catalytic Enantioselective Amination of Alcohols by the Use of Borrowing Hydrogen Methodology: Cooperative Catalysis by Iridium and a Chiral Phosphoric Acid

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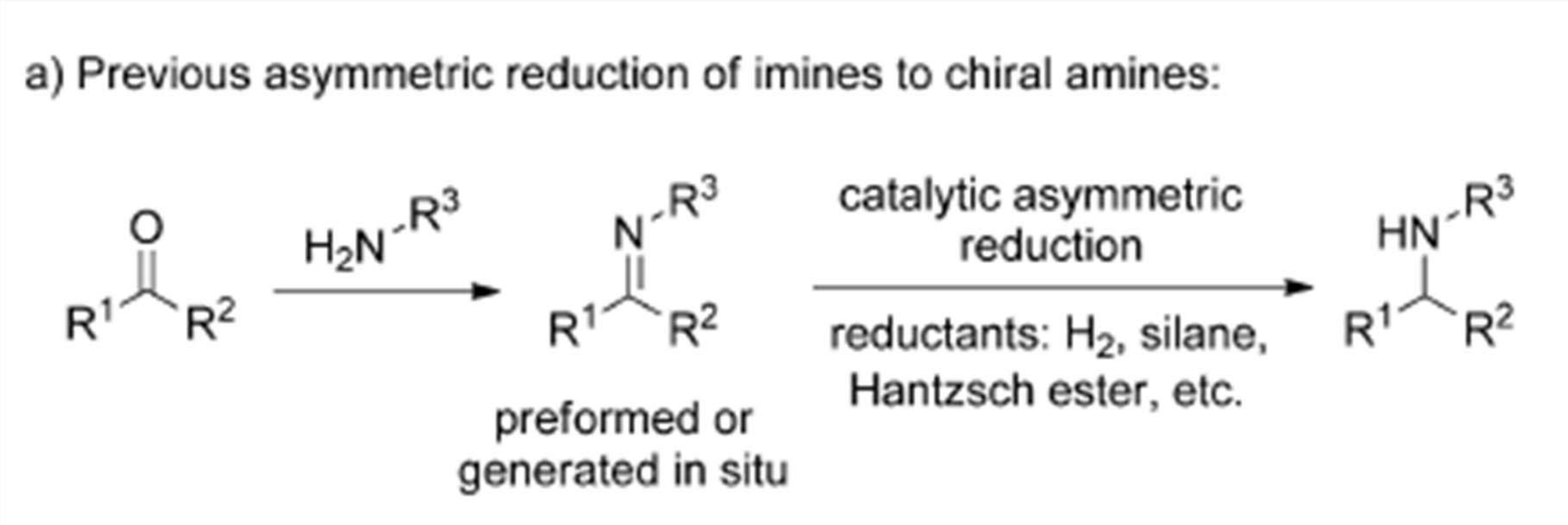
by Haiying Du

6th *Jan* 2014

Introduction



a) H.-U. Blaser, C. Malan, B. Pugin, F. Spinder, H. Steiner, M. Studer, Adv. Synth. Catal. 2003, 345, 103 –151;
b) T. C. Nugent, M. El-Shazly, Adv. Synth. Catal. 2010, 352, 753 – 819;
c) D.-S.Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, Chem. Rev. 2012, 112, 2557 – 2590.

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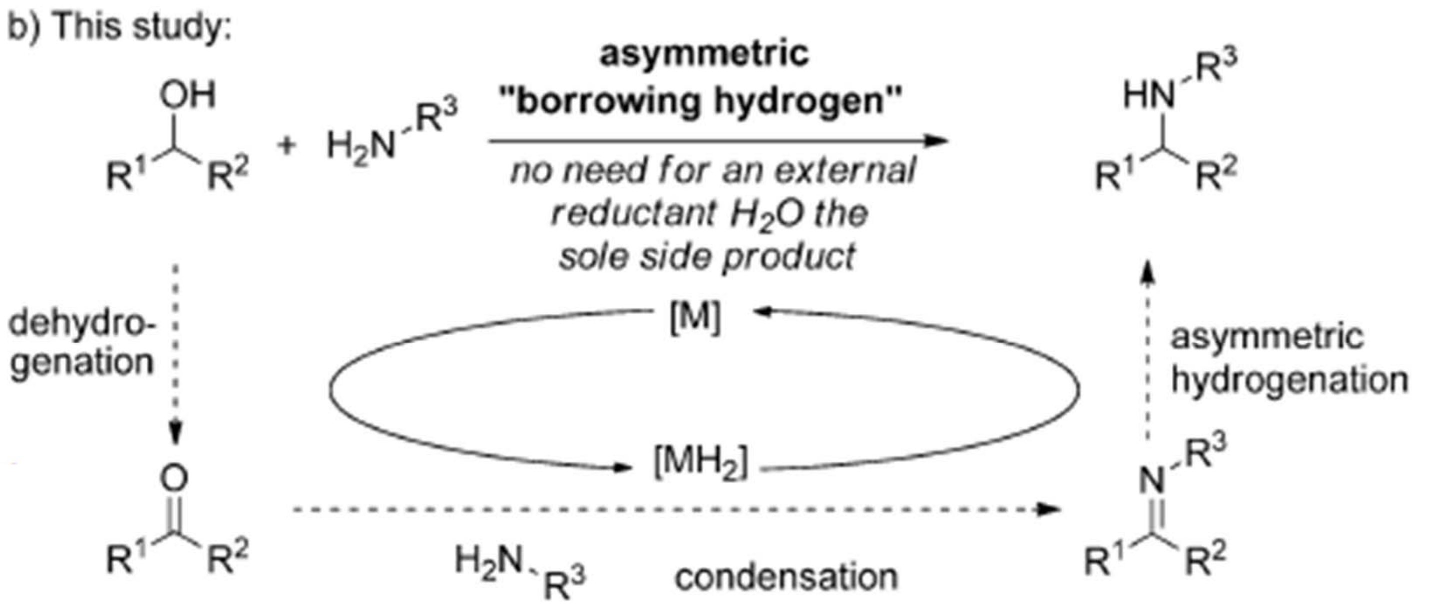
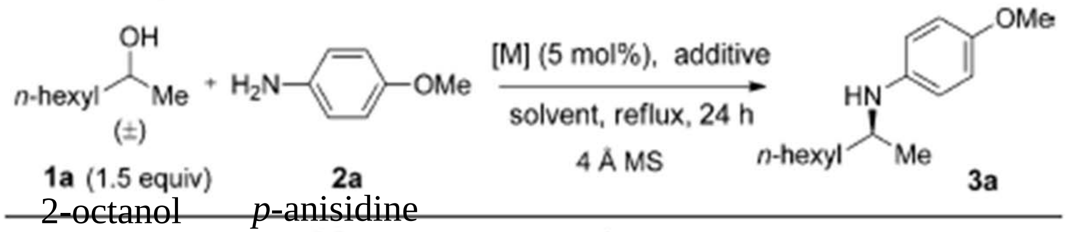


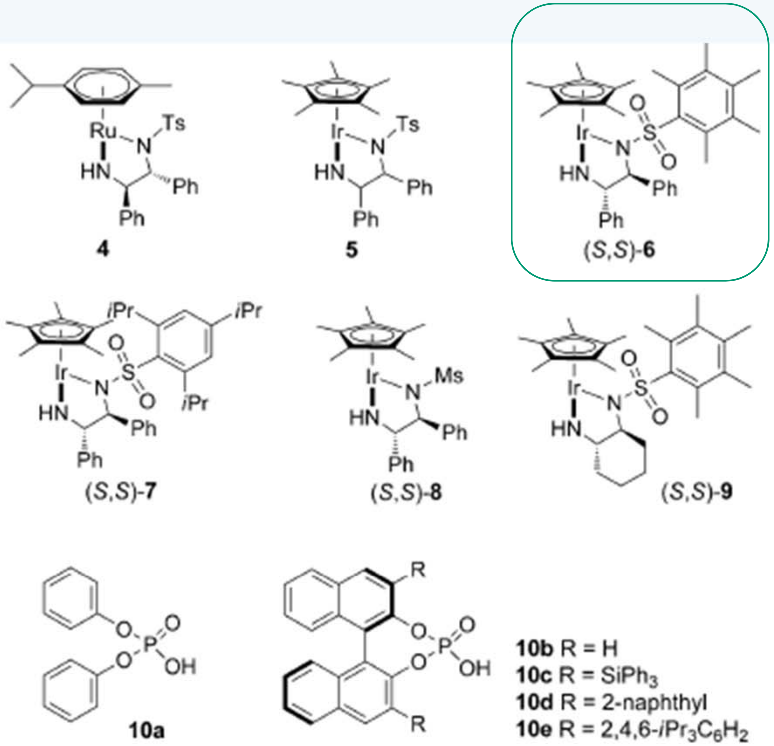
Scheme 1. Different strategies for the synthesis of chiral amines.

the first enantioselective amination of alcohols by the use of borrowing hydrogen methodology under the catalysis of a chiral Ir complex in cooperation with a chiral phosphoric acid

Table 1: Optimization of the enantioselective amination of **1a**.

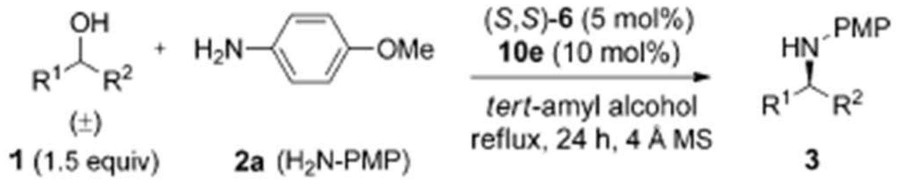


Entry	[M]	Additive	Solvent	Conv. [%][a]	ee [%][b]
1	(*R*,*R*)-**4**	–	toluene	<5	N.D.
2	(*R*,*R*)-**5**	–	toluene	<5	N.D.
3	(*R*,*R*)-**4**	TfOH (5 mol%)	toluene	<5	N.D.
4	(*R*,*R*)-**5**	TfOH (5 mol%)	toluene	32	7
5	(*R*,*R*)-**5**	**10a** (5 mol%)	toluene	33	12
6	(*R*,*R*)-**5**	**10b** (5 mol%)	toluene	60	9
7	(*R*,*R*)-**5**	**10c** (5 mol%)	toluene	<5	N.D.
8	(*R*,*R*)-**5**	**10d** (5 mol%)	toluene	83	−17
9	(*R*,*R*)-**5**	**10e** (5 mol%)	toluene	50	−46
10	(*S*,*S*)-**5**	**10e** (5 mol%)	toluene	32	87
11	(*S*,*S*)-**6**	**10e** (5 mol%)	toluene	>99	81
12	(*S*,*S*)-**7**	**10e** (5 mol%)	toluene	96	77
13	(*S*,*S*)-**8**	**10e** (5 mol%)	toluene	<5	N.D.
14	(*S*,*S*)-**9**	**10e** (5 mol%)	toluene	<5	N.D.
15[c]	(*S*,*S*)-**6**	**10e** (5 mol%)	toluene	>99	90
16[d]	(*S*,*S*)-**6**	**10e** (5 mol%)	toluene	>99	92
17	(*S*,*S*)-**6**	**10e** (5 mol%)	*tert*-amyl alcohol	95	89
18	(*S*,*S*)-**6**	**10e** (10 mol%)	*tert*-amyl alcohol	**>99**	**93**



(c) 3 equivalents of the alcohol, (d) 5 equivalents of the alcohol

Table 2: Scope of the enantioselective amination with respect to the alcohol substrate.[a]

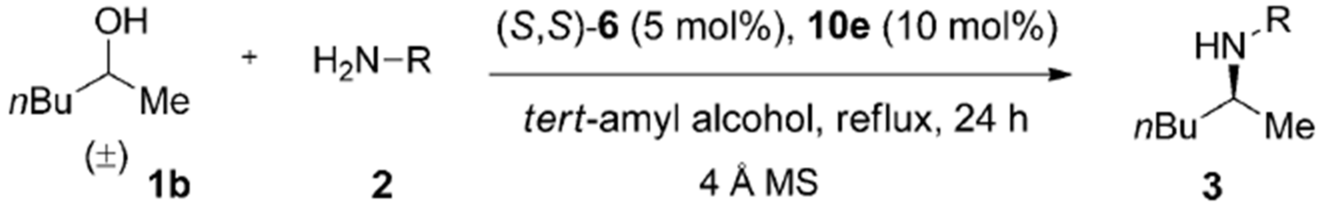


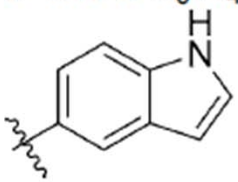
Entry	R^1	R^2	Product	Yield [%][b]	*ee* [%]
1	*n*-hexyl	Me	**3a**	90	93
2[c]	*n*Bu	Me	**3b**	90	92
3[d]	*n*Pr	Me	**3c**	86	90
4	*i*Pr	Me	**3d**	88	96
5	cyclohexyl	Me	**3e**	92	97
6	cyclopropyl	Me	**3f**	93	91
7	$i\text{PrCH}_2$	Me	**3g**	75	82
8	$PhCH_2CH_2$	Me	**3h**	98	83
9	$BnO(CH_2)_3$	Me	**3i**	64	85
10	$TBSO(CH_2)_3$	Me	**3j**	95	91
11	Ph	Me	**3k**	81	91
12	4-MeC_6H_4	Me	**3l**	97	91
13	4-$MeOC_6H_4$	Me	**3m**	72	96
14	4-BrC_6H_4	Me	**3n**	69	83
15	4-$CF_3C_6H_4$	Me	**3o**	90 (40)[e]	70 (94)[e]
16	3-MeC_6H_4	Me	**3p**	83	94
17	1-naphthyl	Me	**3q**	80	94
18	4-MeC_6H_4	Et	**3r**	75	73
19	1-naphthyl	Et	**3s**	71	69
20[f]	*i*Pr	Et	**3t**	80	75

[e] The values in parentheses refer to the corresponding reaction carried out at 80 °C for 48 h.

Contents

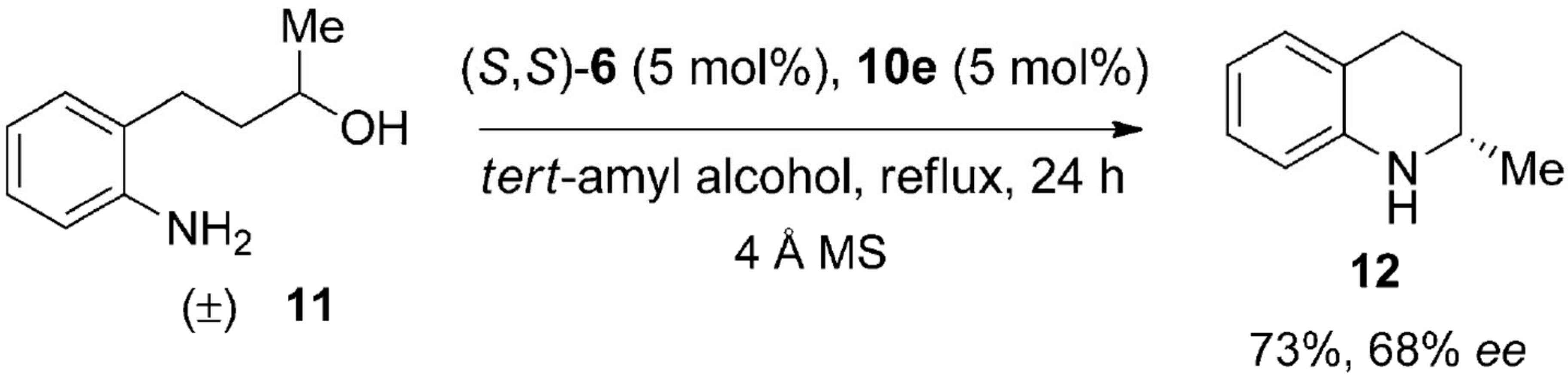
Table 3: Scope of the enantioselective amination with respect to the amine substrate.[a]



Entry	R	Product	Yield [%][b]	*ee* [%]
1	Ph	**3u**	91	88
2	4-MeC_6H_4	**3v**	97	91
3	4-ClC_6H_4	**3w**	81	83
4	4-PhC_6H_4	**3x**	98	89
5	3-$MeOC_6H_4$	**3y**	95	88
6		**3z**	84	81

[a,b] See Table 2.

Contents



Quinoline product

Scheme 2. Example of the intramolecular amination of alcohols.

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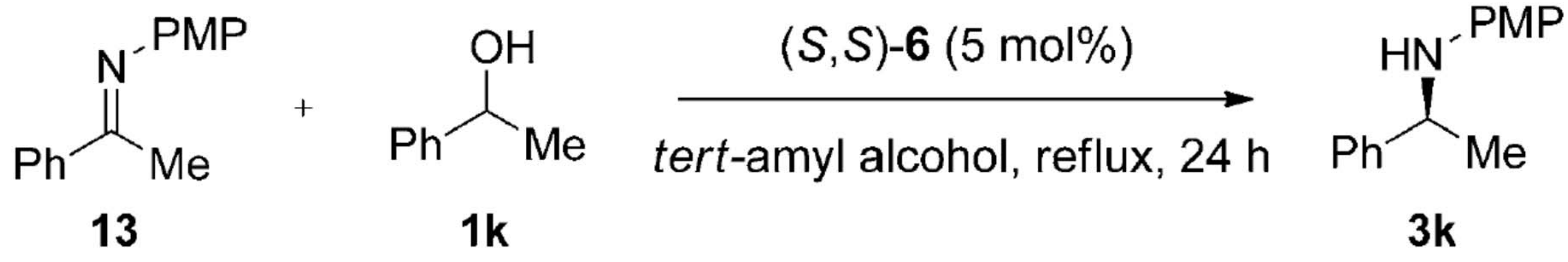
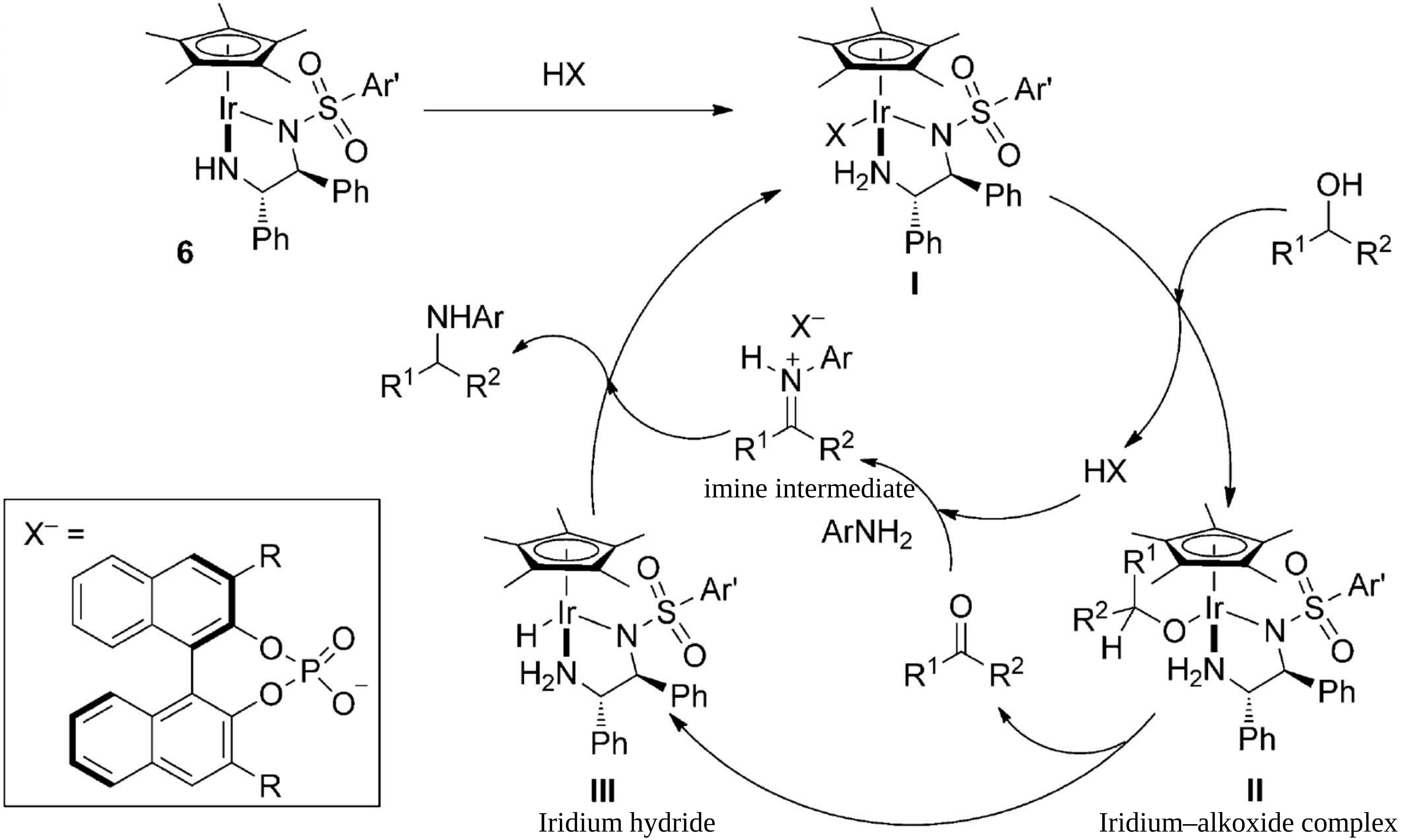
Table 4: Transfer hydrogenation of a preformed imine.



Entry	Amount of **1k** [equiv]	**10e** [mol%]	Yield [%]	*ee* [%]
1	2.0	–	13	<5
2	2.0	10	>95	60
3	10.0	10	>95	71

Alcohol as the hydrogen donor



Scheme 3. Proposed catalytic cycle.


Thanks for your attention!
Happy New Year!!!