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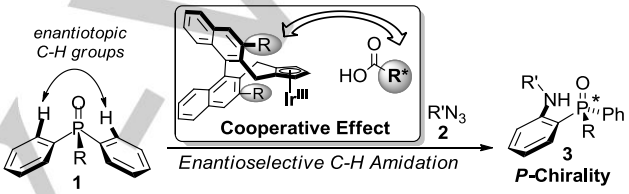
Cooperative Effects between Chiral Cp^xIr^{III} Catalysts and Chiral Carboxylic Acids in Enantioselective C-H Amidations of Phosphine Oxides

Yun-Suk Jang,[a] Michael Dieckmann[a] and Nicolai Cramer*[a]

Abstract: An enantioselective C-H amidation of phosphine oxides by using an iridium(III) catalyst bearing an atropchiral cyclopentadienyl (Cp^x) ligand is reported. A very strong cooperative effect between the chiral Cp^x ligand and a phthaloyl *tert*-leucine enabled the transformation. Matched-mismatched cases of the different acid enantiomers are shown. The amidated *P*-chiral arylphosphine oxides are formed in yields of up to 95 % and with excellent enantioselectivities of up to 99:1 er. Enantiospecific reduction provides access to valuable *P*-chiral phosphorus(III) compounds.

Organophosphorus compounds are a ubiquitous and critically important class of molecules with widespread applications in many fields. For instance, chiral phosphorus(III) compounds are a cornerstone of asymmetric catalysis[1, 2] Phosphorus(V) compounds have been used as Lewis bases[3] or Bronsted acids.[4] *P*-Stereogenic molecules having a stereogenic phosphorus atom are of great interest.[5] Enantiomerically pure *P*-chiral compounds were traditionally obtained through different auxiliary[6] and resolution based methods.[7] More recently, catalytic asymmetric methods have been devised.[8] However, these often suffer from scope limitations, harsh conditions and other shortcomings. The development of efficient catalytic enantioselective procedure leading to chiral *P*-chiral compounds is a highly desirable goal and enantioselective C-H functionalizations of phosphorous-containing substrates offer vast opportunities.[9] For example Chang's achiral Cp^*Ir^{III}-catalyzed C-H amidations[10] result in functionalized molecules that could be elaborated further into valuable *P*,*N*-ligands. However, catalytic-enantioselective iridium-catalyzed C-H amidations are an unsolved challenge.[11] Chang *et al.* reported an asymmetric amidation with the achiral Cp^*Ir^{III} complex in conjunction with a tartaric acid additive, resulting in low enantioselectivities with a maximum of 32 % *ee* on two substrates.[10j] Recently, atropchiral cyclopentadienyl (Cp^X) ligands[12] have proven highly valuable in asymmetric catalysis, especially for ruthenium[13] and rhodium^{III}-catalyzed C-H functionalizations.[9f, 14] For related Cp^xIr^{III} complexes only an enantioselective cycloisomerization was reported,[15] leaving a large untapped potential. Herein, we report a highly selective C-H amidation of phosphine oxides **1** with azides **2** to provide access to *P*-chiral compounds **3** (Scheme 1).



Scheme 1. Enantioselective C–H amidations enabled by a cooperative effect of a chiral Cp^xIr^{III} / chiral carboxylic acid pair.

Chang's proposed catalytic cycle for the Ir^{III}-catalyzed C-H amidation allows identification of key controlling parameters for the design of an enantioselective transformation (Scheme 2).[10j] Initially, dicationic iridium complex **I** is obtained by iodide abstraction from dimeric $(IrCp^XI_2)_2$ complex with $AgNTf_2$. In the presence of carboxylic acids, **I** is in equilibrium with its related monocationic species **II** bearing one carboxylate group. Subsequent coordination to the Lewis-basic carbonyl group of the phosphine oxide substrate gives species **III**. A rate-limiting and enantiodetermining cyclometalation presumably operating by concerted metalation deprotonation (CMD) mechanism[16, 17] yields iridacycle **IV** possessing now a stereogenic center at the phosphorus atom. Subsequent coordination of azide (**V**), followed by migratory insertion proceeding with expulsion of nitrogen, delivers species **VI**. Finally protodemetalation releases amidated product **3** and regenerates catalyst **II**. Since both the Cp^X ligand and the carboxylic acid are coordinated to the iridium metal at intermediate **III**, we hypothesized that a synergistic effect between the two chirality sources could enhance the transmission of the chiral information onto the substrate.

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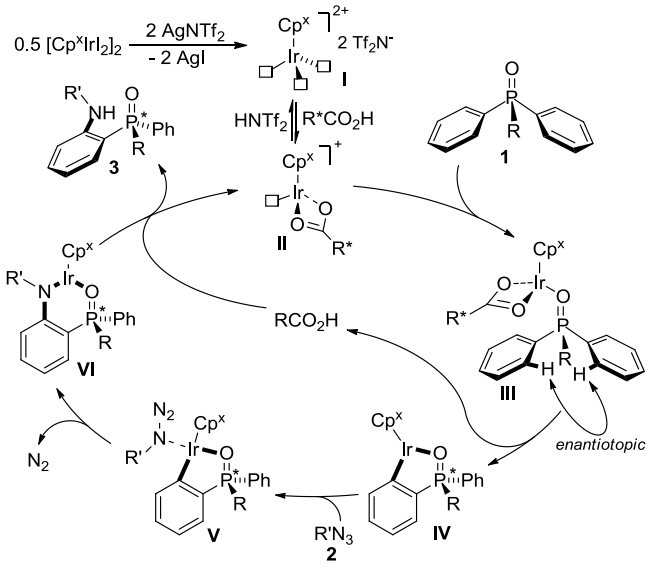
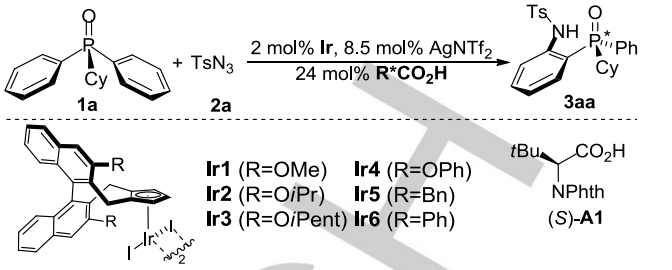


Scheme 2. Catalytic cycle for the asymmetric Ir^{III} C-H amidation.

The enantioselective C-H amidation was initially investigated with diphenyl cyclohexyl phosphine oxide (**1a**) and tosyl azide (**2a**) (Table 1). Iridium catalyst **Ir1** provided in conjunction with pivalic acid product **3aa** in 98 % yield and a modest enantioselectivity of 64.5:35.5 er (entry 1). Switching to chiral carboxylic acid (*S*)-**A1** (*vide infra* for a detailed study of the carboxylic acid effect on this transformation) and lowering the reaction temperature to 23 °C increased gave **3aa** in 83:17 er (entry 2). The selectivity was further improved in dioxane (entry 3). *tert*-Amyl alcohol as a solvent afforded product **3aa** in 95:5 er, albeit with sluggish reactivity due to poor solubility of the iridium catalyst (entry 4). A *tert*-amyl alcohol dioxane mixture solved this problem, providing **3aa** in 83 % yield and 96:4 er at a reaction temperature of 0 °C (entry 5). Using *rac*-**A1** gave 93.5:6.5 er with a reduced conversion and yield (entry 6). Control runs confirmed that the iridium catalyst, $AgNTf_2$ and the carboxylic acid are essential for the transformation (entries 7-9). Rechecking pivalic acid with the otherwise optimized conditions resulted in a low yield and 65:35 er (entry 10) confirming the critical importance of chiral acid (*S*)-**A1**. Using (*S*)-**A1** with achiral Cp^*Ir^{III} catalyst resulted in very poor yield of **3aa** and marginal enantioselectivity (entry 11), underlining once more the synergistic effect between the chiral acid and the chiral Cp^x ligand. Several additional Cp^x ligands were evaluated. Increasing the size of the substituents R (O*i*Pr, O*i*Pent, OPh) caused a decrease in yield, while the enantioselectivity remained high (entries 12-14). Benzyl (**Ir5**) and phenyl substituted ligand (**Ir6**) were neither active nor selective (entries 15-16).

Table 1. Optimization of the conditions for the asymmetric C-H amidation.[a]

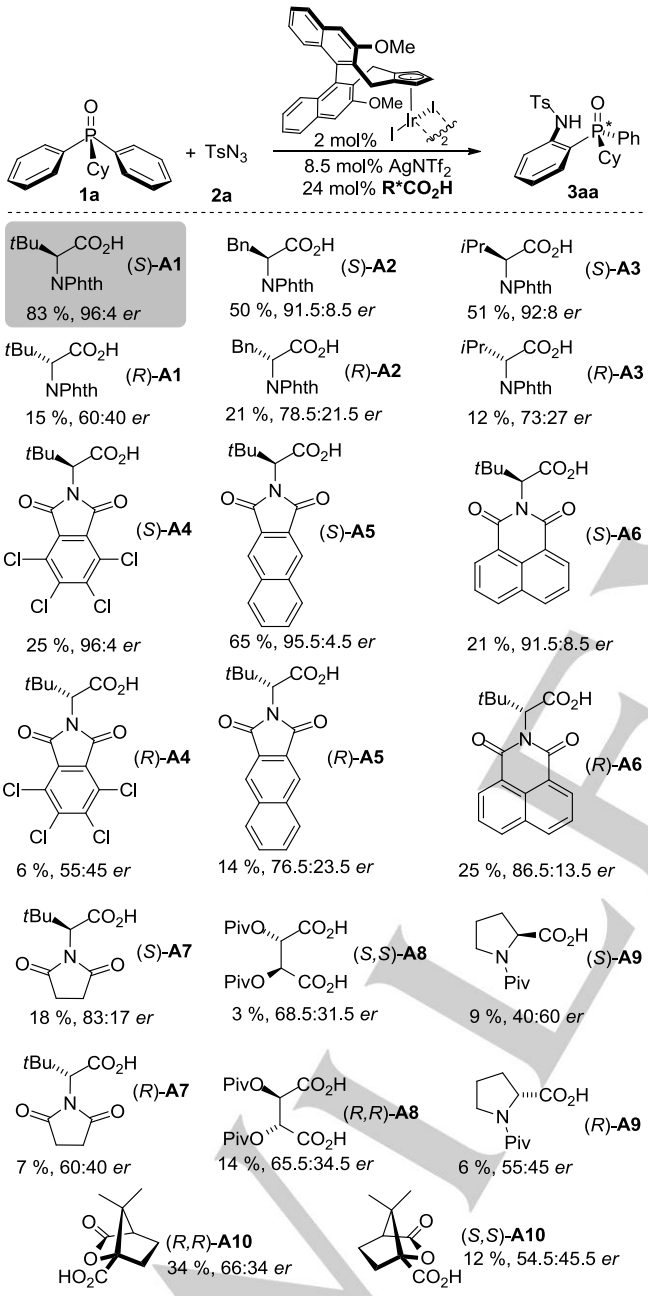


Entry	Ir	Solvent	Additive	T [°C]	Yield [%][b]	er
1[c]	**Ir1**	DCE	PivOH	40	98	64.5:35.5
2[c]	**Ir1**	DCE	(*S*)-**A1**	23	72	83:17
3[c]	**Ir1**	dioxane	(*S*)-**A1**	23	89	87.5:12.5
4[d]	**Ir1**	*t*AmOH	(*S*)-**A1**	10	36	95:5
5	**Ir1**	**S1**	(*S*)-**A1**	0	83[e]	96:4
6	**Ir1**	**S1**	*rac*-**A1**	0	53	93.5:6.5
7	-	**S1**	(*S*)-**A1**	0	0	n.a.
8	**Ir1**	**S1**	-	0	0	n.a.
9	**Ir1**	**S1**	no $AgNTf_2$	0	0	n.a.
10	**Ir1**	**S1**	PivOH	0	19	65:35
11	$[Cp^*IrI_2]_2$	**S1**	(*S*)-**A1**	0	3	52:48
12	**Ir2**	**S1**	(*S*)-**A1**	0	37	94.5:5.5
13	**Ir3**	**S1**	(*S*)-**A1**	0	9	92:8
14	**Ir4**	**S1**	(*S*)-**A1**	0	33	95:5
15	**Ir5**	**S1**	(*S*)-**A1**	0	10	56:44
16	**Ir6**	**S1**	(*S*)-**A1**	0	0	n.a.

[a] Conditions: 50.0 µmol **1a**, 55.0 µmol **2a,** 1.00 µmol **Ir,** 4.25 µmol $AgNTf_2$, 12.0 µmol **R*CO$_2$H,** 36 h, 0.1 M; [b] NMR yield with internal standard; [c] 18 h; [d] 24 h. [e] twice the scale and isolated yield. **S1** = *t*AmOH / dioxane 4:1

We undertook a study to investigate the cooperative interaction[18] of the chiral Cp^x-metal complex and the chiral carboxylic acid additive[19] in greater detail (Scheme 3). The chiral acid additive is an additional and simple handle to tweak yield and selectivity with a small set of chiral Cp^x ligands. *tert*-Leucine derived acid [(*S*)-**A1**] performed better in all parameters than any other chiral carboxylic acids tested. The opposite enantiomer (*R*)-**A1** was not only dramatically less reactive (15 % *vs* 80 % yield), but resulted in a significantly eroded enantioselectivity (60:40 er *vs* 96:4 er). This was evidence for a strong matched-mismatched effect between the Cp^x ligand and the acid. The *S*-enantiomers of phthaloyl-protected acids, derived from phenyl alanine (**A2**) or valine (**A3**), were inferior to **A1**, but still provided product **3aa** in 50 % yield and 92:8 er. Again, the *R*-enantiomers were much less reactive and selective. The phthaloyl protecting group displayed a very pronounced influence on the reactivity. Any replacement, by closely related congeners [(*S*)-**A4**, (*S*)-**A5**, (*S*)-**A6**, (*S*)-**A7**] dramatically reduced

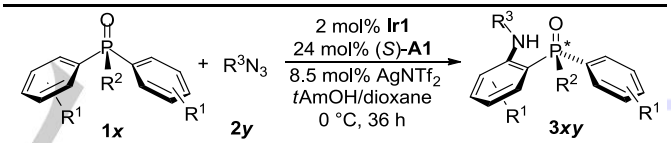
the conversion and yield, while the selectivity remained relatively stable at high levels. In comparison, a selection of other chiral carboxylic acids (**A8**-**A10**) was not suitable at all. With the countless number of commercial carboxylic acids in addition to the ones obtainable in a single step from amino acids, one should be able to identify even better performing examples in the future.



Scheme 3. Matched and mismatched effects of the chiral carboxylic acid additive on the reactivity and selectivity of the C-H amidation.

Next, the scope of the transformation was explored (Table 2). It proceeded well with substrates bearing substituents in the *para*-position (entries 2, 5-8). The enantioselectivities are independent of R^1, with a narrow range from 96:4 to 98.5:1.5 er. Substrates with electron-rich arenes were more reactive than electron-poor ones. *meta*-Substituted arenes reacted selectively with the sterically less hindered *ortho*-C-H group (entries 3 and 6). The reaction is sensitive to bulk in the *ortho*-position and no reaction occurred with *o*-methyl bearing **1e** (entry 4). This fact was in agreement with the lack of any double amidation products. R^2 was found to have a significant influence on the reactivity and the selectivity. Small groups like methyl cause a sluggish and modestly selective amidation (entry 9). Increased steric demand R^2= *i*Pr, Cy, *t*Bu, Ad (entries 11, 1, 12-13) steeply improve reaction performance, giving products **3** in good yields and excellent enantioselectivity of up to 98.5:1.5 er. Notably, the most valuable substrates for envisioned product applications (*P*-chiral phosphine ligands or Lewis bases) have exactly such sterically demanding groups R^2. In addition, phosphine amides were found to be suitable substrates, delivering enantioenriched products **3ra** and **3qa** in good yields albeit with a slightly reduced enantioselectivity (entries 16-17). Finally, different sulfonyl azides were shown to be competent (entries 18-26). Almost no change in reactivity and selectivity was found. The readily cleavable *o*-nosyl group can be introduced with ease (entry 18). With a slightly less reactive substrate like **1i**, *para*-methoxy sulfonyl azide as most electron-rich congener was the best performer giving **3ie** in 75 % yield and 98:2 er (entry 25). X-ray crystallographic analysis of **3aa** unveiled that the absolute configuration of the products was (*R*).[20]

Table 2. Scope for the enantioselective phosphine oxide amidation.[a]

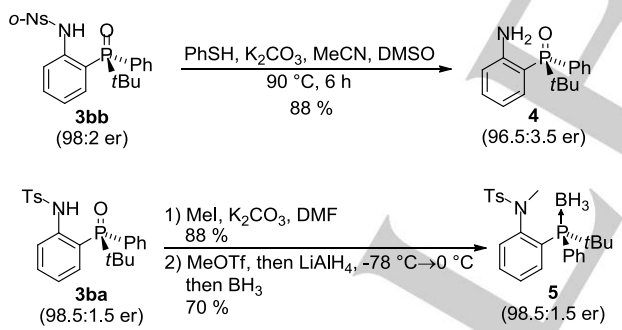


Entry	**3xy**	R^1	R^2	R^3	% Yield[b]	er
1	**3ba**	H	*t*Bu	Ts	95	98.5:1.5
2	**3ca**	*p*-Me	*t*Bu	Ts	87	97.5:2.5
3	**3da**	*m*-Me	*t*Bu	Ts	72	96:4
4	**3ea**	*o*-Me	*t*Bu	Ts	0	n.a.
5	**3fa**	*p*-MeO	*t*Bu	Ts	76	97.5:2.5
6	**3ga**	*m*-MeO	*t*Bu	Ts	79	97:3
7	**3ha**	*p*-NMe_2	*t*Bu	Ts	80	98:2
8[c]	**3ia**	*p*-Cl	*t*Bu	Ts	75	97:3
9	**3ja**	H	Me	Ts	12	70:30
10	**3ka**	H	Bn	Ts	39	88.5:11.5
11[c]	**3la**	H	*i*Pr	Ts	43	95.5:4.5
12	**3ma**	*p*-OMe	Cy	Ts	55	97.5:2.5
13	**3na**	*p*-Me	Cy	Ts	68	93.5:6.5
14	**3oa**	*p*-Cl	Cy	Ts	27	92:8

15	**3pa**	H	Ad	Ts	91	98:2
16	**3qa**	H	N(*i*Pr)$_2$	Ts	60	84.5:15.5
17	**3ra**	H	N(CH$_2$)$_5$	Ts	74	78.5:21.5
18	**3bb**	H	*t*Bu	*o*-Ns	92	98:2
19	**3bc**	H	*t*Bu	*p*-Ns	85	98:2
20[c]	**3bd**	H	*t*Bu	*p*-Cl-C$_6$H$_4$SO$_2$	85	99:1
21	**3be**	H	*t*Bu	*p*-MeO-C$_6$H$_4$SO$_2$	90	98.5:1.5
22	**3bf**	H	*t*Bu	Ms	81	98:2
23[c]	**3ib**	*p*-Cl	*t*Bu	*o*-Ns	42	97:3
24[c]	**3id**	*p*-Cl	*t*Bu	*p*-Cl-C$_6$H$_4$SO$_2$	61	99:1
25[c]	**3ie**	*p*-Cl	*t*Bu	*p*-MeO-C$_6$H$_4$SO$_2$	72	98:2
26[c]	**3if**	*p*-Cl	*t*Bu	Ms	43	95:5

[a] Conditions: 0.1 mmol **1*x***, 0.11 mmol of **2*y***, 2.00 µmol **Ir1**, 8.50 µmol $AgNTf_2$, 24.0 µmol (*S*)-**A1**, 0.1 M in *t*AmOH/dioxane (4:1), 0 °C for 36 h; [b] Isolated yield; [c] with 4.00 µmol **Ir1** and 17.0 µmol $AgNTf_2$.

Removal of the *o*-nosyl group of **3bb** proceeded smoothly under Fukuyama-conditions,[21] providing free aniline **4** in 88% yield with a preservation of the enantiomeric purity (Scheme 4). An enantiospecific reduction of the phosphine oxide functionality of **3ba** was achieved in a two-step procedure.[22] Methylation, followed by treatment with MeOTf and $LiAlH_4$ gave *P*-chiral phosphine (isolated as its borane adduct **5**) without loss of enantiomeric purity.



Scheme 4. *o*-Nosyl-deprotection of **3bb** and enantiospecific reduction of **3ba**.

In summary, we have developed a highly enantioselective C-H amidation of phosphine oxides showcasing the potential of our chiral Cp^x ligand for iridium(III) catalyzed C-H functionalizations. A very strong cooperative effect between the chiral Cp^x ligand and the readily available phthaloyl *tert*-leucine enabled this transformation. We have shown that matched-mismatched cases of the different acid enantiomers can dramatically enhance yield and selectivity. Enantiospecific reduction provides access to valuable *P*-chiral phosphines for potential application as ligands and catalysts.

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Keywords: Asymmetric Catalysis • C–H Activation • Iridium • Chiral Cp Ligand • P-Chirality

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[20] CCDC 1568473 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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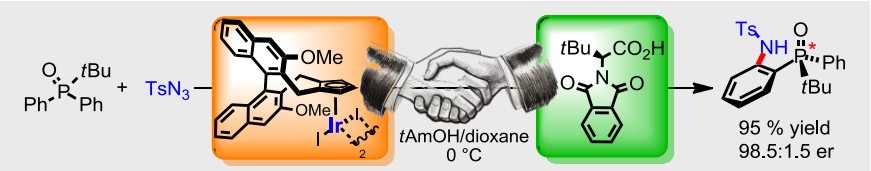

A cooperative effect between a chiral Cp^xIr^{III} complex and chiral carboxylic acid enables highly enantioselective C-H amidations of phosphine oxides with up to 99:1 er. Matched-mismatched pairs have a dramatic influence on the reactivity and the selectivity.

*Yun-Suk Jang, Michael Dieckmann and Nicolai Cramer**

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Cooperative Effects between Chiral Cp^xIr^{III} Catalysts and Chiral Carboxylic Acids in Enantioselective C-H Amidations of Phosphine Oxides