

Asymmetric Synthesis

Iridium(III)-Catalyzed C—H Amidation of Arylphosphoryls Leading to a *P*-Stereogenic Center

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Dedicated to Professor C.-M. Yu on the occasion of his 60th birthday

Abstract: Direct C–H amidation of arylphosphoryl compounds has been developed by using an Ir^{III} catalyst system under mild conditions. A wide range of substrates could be employed with high functional-group tolerance. This procedure was successfully applied for the first time to the asymmetric reaction giving rise to a P-chirogenic center with a high diastereomeric ratio of up to 19:1 (90% *de*).

notable advance in the preparation of chiral phosphorus compounds, the methods presently available often suffer from limited scope, multiple steps, requirement of optical resolution, or harsh reaction conditions. In this regard, the development of a more efficient and stereoselective procedure leading to chiral phosphorus compounds is highly desirable.

To address this issue, an asymmetric induction of the *P*-chiral center was envisioned to be achieved through diastereoselective C–H activation (Scheme 1),^[8,9] and its results are described herein. We have developed an efficient iridium catalyst system

Organophosphorus compounds containing P–C and P–X bonds (X=O, N, S, etc.) have long belonged to an important class of molecules because of their wide applications in medicinal,^[11] materials,^[2] and synthetic chemistry.^[3] This versatility can probably be attributed to their intrinsic nature of having multiple oxidation states of the phosphorus atom and ubiquity in biological systems.^[4] Undoubtedly, *P*-chiral phosphorus compounds draw special attention since they are a key motif consisting of important molecules in pharmaceuticals, agrochemicals, materials, ligands,

and organocatalysts.^[5] In particular, the use of *P*-stereogenic compounds as chiral ligands or catalysts has stimulated the remarkable advance of asymmetric chemistry.^[6] In this aspect, a number of conventional routes has been devised for the synthesis of *P*-chiral compounds. For instance, methods using chiral auxiliary-based diastereomeric resolution, chiral basemediated asymmetric deprotonation followed by addition to electrophiles, or enzymatic desymmetrization of prochiral phosphorus compounds have been investigated.^[7] Enantiose-lective alkylation and alkoxylation of racemic phosphines using chiral Ru or Pd complexes are also known.^[7c-e] Despite of the

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Scheme 1. Our approach in the asymmetric C–H amidation leading to a P-chiral center.

to differentiate two diastereotopic aryl groups of diarylphosphoryl bearing a chiral auxiliary whereby the corresponding *P*chiral products could be attained with up to 90% diastereomeric excess under mild conditions (ratio of two diastereomers, 19:1).

We first tried to optimize direct C–H amidation conditions initially using triphenylphosphine oxide (1) as a model substrate in a reaction with *p*-toluenesulfonyl azide (TsN₃, 1.1 equiv). After extensive studies (see the Supporting Information for details),^[10] we found that the addition of pivalic acid (PivOH, 12 mol%) was essential for promoting the amidation with the combined use of [IrCl₂(Cp*)]₂ (2 mol%; Cp* = 1,2,3,4,5pentamethylcyclopentadiene) and AgNTf₂ (8.5 mol%) leading to the desired amidated product **2** in 84% yield [Eq. (1)].^[11] An X-ray diffraction analysis of **2** revealed that an intramolecular H-bonding exists between P=O and N*H*Ts moieties. In addition, a bis-amidated compound **3** was also formed (5%), and its solid structure was also characterized to confirm that the second amidation occurred at a different phenyl ring.

With the optimal amidation conditions in hand, we were next encouraged to undertake an asymmetric amidation study (Table 1). Initially, we hypothesized that diarylphosphoryl compounds bearing chiral auxiliaries would be a plausible template

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to lead to the diastereoselective formation of a key five-membered iridacycle by the $|r^{III}$ -mediated asymmetric C–H bond activation on two diastereotopic aryl rings to give rise to *P*-chirality (Scheme 1). As a reference, when a nonchiral substrate (**4a**) was reacted with a chiral azide, for example, (1*S*)-(+)-camphorsulfonyl azide, amidation took place with a low diastereomeric ratio (52:48, **4**). Similarly, a low level of diastereomeric excess (*de*) was observed in a reaction of diphenylphosphinic amide (**5a**) to afford **5** (6% *de*) in a reaction with the chiral azide. This result ascertains our working hypothesis that an asymmetric induction arises from a C–H bond cleavage step rather than in an azide insertion stage. Interestingly, a reaction of diphenyl(binaphthyl)phosphine oxide (**6a**), wherein binaphthyl is axially chiral, occurred exclusively at the binaphthyl moiety instead of two phenyl rings, thereby **6** was not *P*-chiral.

We then proceeded to explore a stereoselective C-H amidation by using diarylphosphorus compounds possessing chiral auxiliaries. When diphenylphosphine oxide bearing a chiral alkoxy group, for example, (-)-menthol, was amidated under the standard conditions, a desired product (7) was obtained with a diastereomeric ratio of 62:38 (24% de). Although this selectivity was not satisfactory, it encouraged us to further search for more appropriate substrates that allow for higher diastereoselectivity. Indeed, it was shown that the change of an alcohol auxiliary led to improved stereoselectivity: 8a was smoothly amidated to give 8 with 41% de at 85°C and 48% de at 55°C. The higher de in 8 than that in 7 implies that a phenyl moiety on the chiral auxiliary could affect the diastereoselection step presumably by $\pi - \pi$ interactions with aryl rings on the P atom (vide infra).^[12] The diaryl part of substrates was next modified by electronically different substituents. When a p-methoxy group was substituted, diastereoselectivity of the obtained product (9) was 44% de under the standard conditions (85 °C), and increased to 62% de at 50°C (1 mol% of Ir catalyst). A para-chloro-substituted substrate (10a) was amidated slowly with 49% de at 85°C

(58% *de* at 55 °C). However, the introduction of substituents at the *ortho*-position on the aryl rings resulted in lower diastereoselectivity as seen by **11** and **12**.

The observation that diastereoselectivity changed to some extent depending on the substituent type in substrates led us to study this pattern more quantitatively. For this purpose, amidation of four substrates (**10a**, **8a**, **9a**, and **12a**) was performed at incremental temperatures between 25 and 85 °C over 4 to 96 h (Table 2). Four sets of plots of ln(d.r.) versus 1/T were obtained with excellently linear regressions ($R^2 > 0.99$), which implied that the diastereoselective amidation takes place through a common mechanistic pathway at each temperature range (see the Supporting Information for details).^[7c]

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Table 2.	Correlation	between	reaction	temperature	and	diastereoselectivity	in t	the a	amidation	of	8a-10a	and
12 a wit	h TsN₃. ^[a]											

Entry	Product	Slope	$\Delta\Delta H^{+}$ [kcal mol ⁻¹]	y-intercept	$\Delta\Delta S^{*}$ [e.u.]	$\Delta\Delta G^{+[b]}$ [kcal mol $^{-1}$]
1	10 (R=4-Cl)	-964.4	1.92	1.61	3.2	0.97
2	8 (R = H)	-781.6	1.55	1.31	2.6	0.78
3	9 (R=4-MeO)	-671.2	1.33	0.94	1.9	0.76
4	12 (R=2-MeO)	-892.1	1.77	2.11	4.2	0.52
				(6 8)] (0.00.		(0.047 1) 01 011

[a] 8a–10a and 12a (0.20 mmol), TsN₃ (0.22 mmol), $[IrCl_2(Cp^*)]_2$ (0.004 mmol), AgNTf₂ (0.017 mmol), PivOH (0.024 mmol) in 1.2-DCE (0.5 mL) for 4 to 96 h at 25 to 85 °C. The d.r. was referred to as a diastereomeric ratio determined based on ³¹P{1H} NMR spectra of a crude reaction mixture. [b] Values at 298 K.

dard conditions (2 mol% of Ir catalyst and 12 mol% of PivOH at 60 °C for 12 h), an enantiomeric product 13-enan was obtained with similar de when compared to 13. Diastereomeric ratio was determined by ³¹P NMR spectroscopy and chiral-HPLC analysis of the crude mixture in this study.

Diastereoselectivity was slightly changed by substituents at the para-position: 14 (82% de; *p*-methyl substituent), 15 (79% de; p-methoxy), and 16

By applying the obtained correlation between temperature and d.r. to a differential Eyring equation, $\ln(d.r.) = -\Delta\Delta H^{+}/RT +$ $-\Delta\Delta S^{\dagger}/R$, we were able to calculate $-\Delta\Delta H^{\dagger}$ and $-\Delta\Delta S^{\dagger}$ for

each set of amidations, ranging from 1.92 to 1.33 kcalmol⁻¹ and from 4.2 to 1.9 e.u., respectively. Notably, it was found that the differential activation parameters $(-\Delta\Delta S^{\dagger}, -\Delta\Delta H^{\dagger}, \text{ and } -\Delta\Delta G^{\dagger})$ increased as electron-withdrawing groups were substituted at the para-position, whereas the values of a substrate containing an ortho-methoxy group (12a) were rather out of the above trend.

Given the preliminary observation that phosphinic amides (e.g. 5a) exhibited excellent reactivity in the current C-H amidation and that an aryl pendant on the chiral auxiliary led to higher diastereoselectivity (Table 1, 7 versus 8), we designed a new type of diarylphoryl bearing a C2-symmetric chiral pyrrolidine moiety^[13] to explore the possibility of inducing P-chirality more effectively (Table 3). A substrate 13a was smoothly amidated at 60°C to give 13 in 84% yield, more significantly, with a diastereomeric ratio of 90:10 (80% de). It was increased to 84% de when the reaction was carried out at 25 °C (24 h). A full conversion was attained in 48 h even with 0.5 mol% of catalyst at 60°C, showing a turnover number of approximately 200. As expected, when a substrate 13a-enan, an enantiomer of 13a, was subjected to the stan(77% de; p-chloro group). Interestingly, it was also influenced to some extent by the azides employed. For example, while the amidation of 17 a with (p-methoxybenzene)sulfonyl azide



(0.024 mmol) in 1,2-DCE (0.5 mL) at 60 °C for 12 h or at 25 °C for 24 h (isolated yields). The *de* was determined based on ³¹P{¹H} NMR spectra of a crude reaction mixture.

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took place with 80% *de* (17), which was identical to product 13 obtained with (*p*-methylbenzene)sulfonyl azide, 90% *de* (18) was observed when benzylsulfonyl azide was reacted.

Slightly lower selectivity was observed with butanesulfonyl azide (88% de of product 19) or (pchlorobenzene)sulfonyl azide (84% de of product 20), in all excellent chemical yields. Diarylphosphinic amides substituted with the p-methyl- or p-methoxy group were amidated with benzylsulfonyl azide to afford 21 (89% de at 60°C and 90% de at 25°C) and 22 (86% de at 60°C and 89% de at 25°C), respectively. Again, it needs to be emphasized that high chemical yields (>90%) were obtained even from room temperature reactions. A similar level of de was observed in a reaction with a chiral azide to give 23 in high yield. It needs to be emphasized to the observed stereochemical outcome is driven presumably by the difference of the secondary interactions as shown in Scheme 2.^[15]



Scheme 2. A plausible pathway leading to the amidated product 13 with a (R)-configuration at the P-center.

that optically pure *P*-chirogenic products were obtained in high yields by a simple purification process from the optically enriched crude reaction mixture.

The absolute configuration at the newly generated *P*-chirogenic center of a major diastereomer of **13** was determined to

be (R) by X-ray crystallographic analysis. Although additional studies are required to reason the origin of the observed diastereochemical outcome at the P-chiral center, it is presently assumed that two aryl groups in diarylphosphinic amide subbecome strates inequivalent during the course of forming the corresponding iridacycles. Indeed, the DFT-optimized structure of 13a indicates that the Pcenter is pseudo-stereogenic because of the different degree of secondary interactions of each phenyl ring on the P atom with phenyl groups of a chiral auxiliary. The solid structure of amidated product 13 revealed that the P-chiral center has a (R)-configuration and that an unamidated phenyl ring displays stronger π - π interactions with a phenyl group in auxiliary.[12,14] Based on these structural features, we tentatively propose that a path of the C–H bond activation leading

Finally, we explored the substrate scope of arylphosphoryl compounds, $Ar_nR_{3-n}P=O$ (R = alkyl, aryl),^[16] which can be an alternative template bearing a alkyl or aryl chiral auxiliary eventually for the perspective asymmetric C–H functionalization (Table 4). A series of triarylphosphine oxides was examined to



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reveal that the direct C–H amidation took place smoothly irrespective of the electronic properties of the substituents (**2**, **24**– **27**).^[17] It was shown that the position of substituents at the aryl rings influenced the reaction efficiency to some extent (**28–30**). The amidation was highly regioselective, occurring at the sterically less demanding C–H bonds (**31**). A reaction of tris(1-naphthyl)phosphine oxide took place selectively at the 2position, and its structure (**32**) was confirmed by X-ray crystallographic analysis. A new type of substrate of diphenyl(monoalkyl)phosphine oxides was also viable for the present C–H amidation that takes place at the aryl group. The corresponding products were obtained in high yields irrespective of the steric bulkiness of the alkyl groups. The structure of **37** was confirmed by X-ray diffraction analysis.

In summary, for the first time we have developed an efficient Ir^{III}-catalyzed asymmetric C–H amidation of arylphosphoryls bearing chiral auxiliaries. Diastereomeric excesses of up to 90% were attained (ratio of two diastereomers, 19:1) with a C_2 -symmetric chiral pyrrolidine auxiliary, and optically pure *P*-chirogenic products could readily be obtained in high yields by a simple purification process. While experimental observations led us to propose the formation of an iridacycle as a diastereo-determining step, a *pseudo*-diastereomeric environment of substrates derived from a different level of secondary interactions was assumed to be the basis for the observed stereo-chemical outcomes.

Experimental Section

Representative procedure

In a 1 mL reaction vial, triphenylphosphine oxide (1) (55.7 mg, 0.20 mmol), $[IrCl_2(Cp^*)]_2$ (3.2 mg, 0.004 mmol), and AgNTf₂ (6.6 mg, 0.017 mmol) were dissolved in 1,2-dichloroethane (1,2-DCE, 0.5 mL) and briefly shaken, to which tosyl azide (TsN₃) (43.4 mg, 0.22 mmol) and pivalic acid (PivOH, 48 µL from 0.5 \bowtie stock solution in 1,2-DCE, 0.024 mmol) were subsequently added. The reaction mixture was stirred at 85 °C for 4 h, and then cooled down to room temperature and filtered through a pad of Celite with ethyl acetate (20 mL). The filtrate was concentrated in vacuo and purified by column chromatography on silica gel (acetone/*n*-hexane = 1:3 and EtOAc/CH₂Cl₂/*n*-hexane = 1:6:4) to give **2** (75.2 mg, 84%).

Keywords: asymmetric induction \cdot C–H functionalization \cdot chirality \cdot iridium catalysis \cdot phosphine oxides

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