Allylic Substitution

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Iridium-Catalyzed Asymmetric Allylic Substitutions—Very High Regioselectivity and Air Stability with a Catalyst Derived from Dibenzo[*a*,*e*]cyclooctatetraene and a Phosphoramidite**

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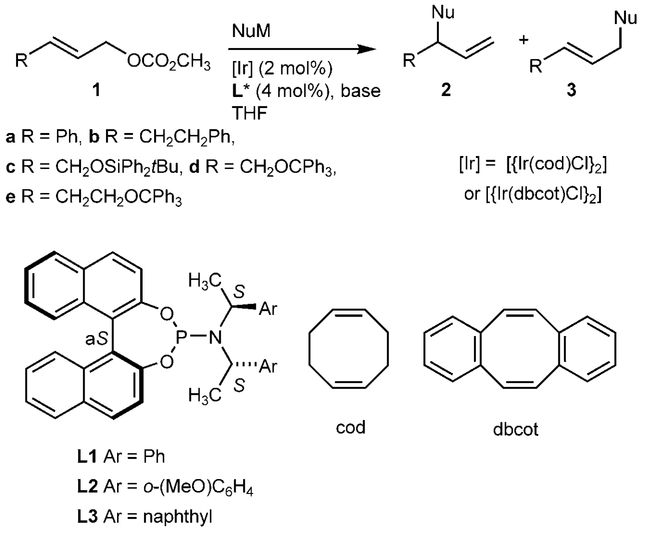
Transition-metal-catalyzed asymmetric allylic substitutions are widely employed. Steric course and regioselectivity of these reactions vary considerably, depending on the metal ion, ligands, the nucleophile, and the leaving group. Today, Pd catalysts[1] are usually employed for 1,3-disubstituted allylic substrates, while Ir catalysts[2] serve well for a broad range of monosubstituted allylic substrates.

The currently best Ir catalysts are prepared from [{Ir(cod)Cl}$_2$] (cod = cycloocta-1,5-diene) and a chiral phosphoramidite by C–H activation with base (Scheme 1). Although enantioselectivity is high, this catalyst system suffers from several deficiencies: 1) It is sensitive towards oxygen. 2) Long-term stability is low. 3) High selectivities are obtained only with solvents of low polarity, preferably THF. The catalyst system is stable against water and alcohols; however, enantioselectivity in these solvents is lower than in THF. 4) Regioselectivity can be as low as 3:1 (**2**/**3**), for example, with substrates **1b**–**e**.[3]

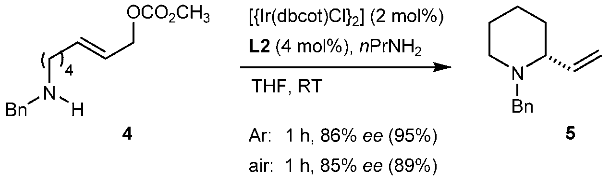


Scheme 1. Ir-catalyzed allylic substitutions.

We have now developed a modified catalyst derived from dibenzo[*a*,*e*]cyclooctatetraene (dbcot) and **L2**, which allows substitutions to be run without inert gas for the first time. In addition, regioselectivities with the new catalyst are considerably improved over those with presently used catalysts. Furthermore, we have observed that catalyst preparation by C–H activation is reversible for complexes of **L2** under the standard reaction conditions.

The ligand cod can be removed from iridium or altered by a number of reactions. For improvement, dbcot appeared promising because its bonding to Ir is stronger than that of cod, its Ir complexes do not undergo intramolecular C–H activation at the dbcot moiety, and it is a better electron acceptor than cod.[4]

Preparations of dbcot[5] and [{Ir(dbcot)Cl}$_2$][4] were straightforward. The latter was subjected to C–H activation under argon by treatment with 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD)[6] or *n*-propylamine (Scheme 3).[7] Substitution reactions were investigated with ligands **L1**–**L3** (Scheme 1); the best results were obtained with **L2**.



Scheme 2. Intramolecular allylic amination.

Regioselectivities of all reactions run under anaerobic conditions with the dbcot complex were considerably improved compared to those run with the cod complex (Table 1).[8] In some cases (entries 9, 11, 15, and 18, Table 1), mostly reactions under salt-free conditions,[9] a reaction temperature of 50 °C was used to shorten the reaction times. This was generally possible without significant loss of selectivity. The enantioselectivity, not the regioselectivity,

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Table 1: Allylic substitutions carried out under argon according to Scheme 1 using catalysts derived from **L2** and [{Ir(cod)Cl}$_2$][8] or [{Ir(dbcot)Cl}$_2$].[a]

Entry	Coligand	Base for C–H activation	Carbonate	(Pro)nucleophile	*T* [°C]	*t* [h]	Yield of **2**+**3** [%][b]	**2**/**3**[c]	*ee* [%][d]
1	cod	*n*PrNH$_2$	**1a**	BnNH$_2$	RT	3	94	96:4	98
2	dbcot	*n*PrNH$_2$	**1a**	BnNH$_2$	RT	3	88	98:2	98
3	dbcot	*n*PrNH$_2$	**1a**	PhNH$_2$	RT	2	95	97:3	98
4[e]	dbcot	*n*PrNH$_2$	**1a**	NaHC(CO$_2$Me)$_2$	RT	4	87	99:1	97
5	dbcot	*n*PrNH$_2$	**1a**	H$_2$C(CO$_2$Me)$_2$	RT	5	77	99:1	98.5
6	cod	*n*PrNH$_2$	**1b**	BnNH$_2$	RT	2	65	85:15	95
7	dbcot	*n*PrNH$_2$	**1b**	BnNH$_2$	RT	3.5	79	96:4	94
8	cod	TBD	**1c**	H$_2$C(CO$_2$Me)$_2$	RT	8	85	76:24	98.5
9	dbcot	TBD	**1c**	H$_2$C(CO$_2$Me)$_2$	50	4	91	94:6	92
10	cod	TBD	**1c**	BnNH$_2$	RT	2	68	73:27	97
11	dbcot	*n*PrNH$_2$	**1c**	BnNH$_2$	50	2	87[f]	>95:5[f]	90
12	cod	TBD	**1d**	*o*-NsNH$_2$	RT	6	79	87:13	94
13	dbcot	TBD	**1d**	*o*-NsNH$_2$	RT	18	85	97:3	93
14	cod	TBD	**1d**	H$_2$C(CO$_2$Me)$_2$	RT	18	90	82:18	99
15	dbcot	TBD	**1d**	H$_2$C(CO$_2$Me)$_2$	50	2	88	94:6	94
16	cod	TBD	**1e**	H$_2$C(CO$_2$Me)$_2$	RT	18	90	74:26	92
17	dbcot	TBD	**1e**	H$_2$C(CO$_2$Me)$_2$	RT	18	95	97:3	95
18	dbcot	TBD	**1e**	H$_2$C(CO$_2$Me)$_2$	50	1	93	93:7	96

[a] Catalyst preparation (Scheme 3): argon atmosphere, [{Ir(cod)Cl}$_2$] or [{Ir(dbcot)Cl}$_2$] (0.01 mmol), **L2** (0.02 mmol), *n*-propylamine (0.3 mmol), THF (0.5 mL), 1 h, 50 °C or TBD (0.04 mmol), THF (0.5 mL), 10 min, RT; substitution reaction: carbonate **1** (0.5 mmol), pronucleophile (0.65 mmol), THF (0.5 mL), RT. Abbreviations: Bn = benzyl, *o*-Ns = *o*-nitrophenylsulfonyl. [b] Yield of isolated product, combined regioisomers. [c] Determined by ^{1}H NMR spectroscopy of the crude products or by isolation of the individual regioisomers. [d] Determined by HPLC with a chiral stationary phase (see the Supporting Information). [e] 2 equiv pronucleophile. [f] The isolated linear product contained ca. 15 % of an unidentified by-product.

Table 2: Allylic substitutions carried out under air according to Scheme 1 using catalysts derived from **L2** and [{Ir(cod)Cl}$_2$] or [{Ir(dbcot)Cl}$_2$].[a]

Entry	Coligand	Carbonate	(Pro)nucleophile	*T* [°C]	*t* [h]	Yield of **2**+**3** [%][b]	**2**/**3**[c]	*ee* [%][d]
1	cod	**1a**	BnNH$_2$	RT	[e]	0	–	–
2	dbcot	**1a**	BnNH$_2$	RT	20	89	99:1	98
3	dbcot	**1a**	BnNH$_2$	50	3	88	99:1	96
4	cod	**1b**	BnNH$_2$	RT	[e]	0	–	–
5	dbcot	**1b**	BnNH$_2$	RT	72	46	94:6	94
6	dbcot	**1b**	BnNH$_2$	50	7	75	92:8	93
7	dbcot	**1a**	PhNH$_2$	RT	2	94	98:2	98
8[f]	dbcot	**1a**	NaHC(CO$_2$Me)$_2$	RT	70	71[g]	98:2	97
9[f]	dbcot	**1a**	NaHC(CO$_2$Me)$_2$	50	1.5	83	95:5	95

[a] Catalyst preparation and conditions as in Table 1; *n*-propylamine was used for C–H activation; then argon was exchanged for air. [b] Yield of isolated product, combined regioisomers. [c] Determined by ^{1}H NMR spectroscopy of the crude products or by isolation of the individual regioisomers. [d] Determined by HPLC with a chiral stationary phase (see the Supporting Information). [e] No reaction after > 70 h. [f] 2 equiv pronucleophile. [g] Corrected yield: 90 %.

was somewhat reduced only in the case of the particularly bulky *t*BuPh$_2$Si-protected carbonate **1c** (entries 8–11, Table 1).

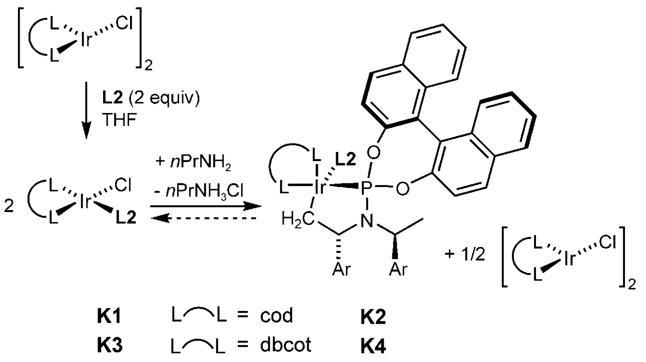
Allylic substitutions with the new catalyst were also possible under aerobic conditions. The results are presented in Table 2. Control experiments using the catalyst derived from [{Ir(cod)Cl}$_2$] and **L2** did not proceed at all under air (entries 1 and 4, Table 2). Reaction times under air were longer than those under argon; however, they could be reduced by running reactions at 50 °C (entries 3, 6, and 9, Table 2); selectivities were only marginally diminished.

The new catalyst was also examined in an intramolecular allylic amination (Scheme 2). With the [{Ir(dbcot)Cl}$_2$]/**L2** catalyst it was possible to carry out the reaction under air to completion within one hour. In this case enantioselectivity was slightly lower than that obtained with [{Ir(cod)Cl}$_2$]/**L2**.[10]

In the course of this work with the new catalyst, we were also able to shed new light on the mechanism of catalyst preparation with the cod and dbcot complexes, building on the mechanistic work of Hartwig et al., which was mainly based on reactions of cod/**L1** complexes.[11] To date it is assumed that C–H-activated species of type **K2**/**K4** are necessary precatalysts (Scheme 3). However, work of the Alexakis group[12] with **L2** showed that good results can be obtained without explicit base activation. Furthermore, Alexakis et al. described the recovery of a catalytically fully active orange powder, which they did not characterize. We identified this compound as the starting complex **K1**. This finding was an incentive to investigate the activation process, both for cod and dbcot complexes, with respect to reversibility.

The orange-colored complex **K1** was prepared according to Scheme 3 and was characterized spectroscopically and by an X-ray crystal structure analysis.[13] The ^{31}P NMR spectrum (Figure 1, I) showed two singlets at $\delta = 121$ and 132 ppm with an intensity ratio of 4:1. The latter resonance correlates with an Ir–H resonance at $\delta = -17$ ppm (doublet, $J = 6$ Hz) in the ^{1}H NMR spectrum; accordingly we propose that in solution an equilibrium exists between **K1** and the hydrido-complex **K1H**.

The reaction of **K1** with *n*PrNH$_2$ (15 equiv, [D$_8$]THF, 50 °C) gave rise to a yellow solution after 1 h (solution A), and the ^{31}P NMR spectrum showed doublets at $\delta = 155$/129 ppm, $J = 47$ Hz, and 152/142 ppm, $J = 72$ Hz, with an intensity ratio of 5:4 (Figure 1, II).[14] Based on the results of Hartwig et al. with ligand **L1**,[15] we assume the new complexes to be **K2** and a diastereomer.



Scheme 3. Base-induced C–H activation. Ar = *o*-(MeO)C$_6$H$_4$.

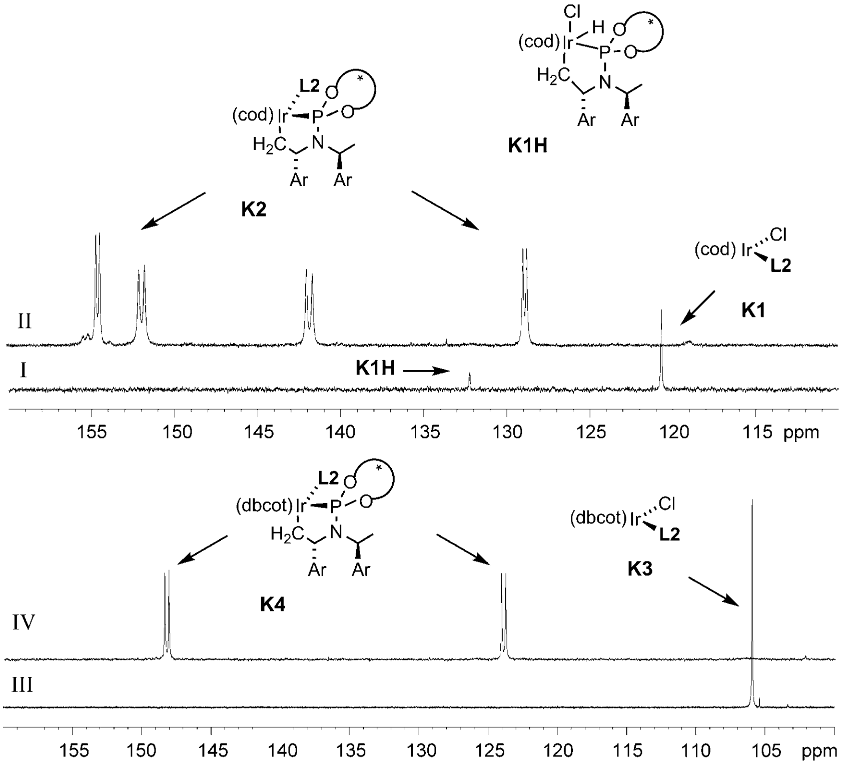


Figure 1. ^{31}P NMR spectra ([D$_8$]THF); I: **K1**, prepared from [{Ir(cod)Cl}$_2$] (10 μmol) and **L2** (20 μmol) in [D$_8$]THF (0.5 mL), RT; II: **K2**, prepared from [{Ir(cod)Cl}$_2$] (10 μmol), **L2** (20 μmol), and *n*PrNH$_2$ (300 μmol) in [D$_8$]THF (0.5 mL), −60 °C; III: **K3**, prepared from [{Ir(dbcot)Cl}$_2$] (10 μmol) and **L2** (20 μmol) in [D$_8$]THF (0.5 mL), RT; IV: **K4**, prepared from [{Ir(dbcot)Cl}$_2$] (30 μmol), **L2** (60 μmol), and *n*PrNH$_2$ (900 μmol) in [D$_8$]THF (0.5 mL), RT. Ar = *o*-(MeO)C$_6$H$_4$.

It is important to note that solution A also contained *n*PrNH$_3$Cl and 0.5 equiv [{Ir(cod)Cl}$_2$]. Upon removal of volatiles in vacuo and dissolving the residual yellow powder in anhydrous [D$_8$]THF, an orange solution was obtained. The ^{31}P NMR spectrum now showed only the signals of **K1**. Clearly, reversal of C–H activation must have occurred. The source of the requisite HCl must have been residual *n*PrNH$_3$Cl not removed by evaporation. This result indicates that an equilibrium exists between **K1** and **K2**. Mild base suffices to shift the equilibrium in the direction of **K2**. In a reaction of **1a** with dimethyl malonate under salt-free conditions **K1** constituted the resting state (NMR). Full conversion of **K2** into **K1** could also be effected with acetic acid (see the Supporting Information).

Corresponding experiments as described above were carried out with dbcot complexes. The complex **K3** was prepared according to Scheme 3 by addition of **L2** (20 μmol) to a solution of [{Ir(dbcot)Cl}$_2$] (10 μmol) in THF (0.5 mL). **K3** was obtained as orange-colored glass. The ^{31}P NMR spectrum (Figure 1, III) showed a singlet at $\delta = 106$ ppm. A hydrido complex analogous to **K1H** was not observed. **K3** was characterized by ^{1}H NMR (TOCSY, NOESY, ROESY) and ^{13}C NMR spectroscopy (HSQC, HMBC) as well as by FAB$^+$ mass spectrometry.

K3 was reacted with *n*PrNH$_2$ under the same conditions as described above for the formation of **K2** in solution A. The resultant yellow solution (solution B) showed the anticipated two doublets, at $\delta = 148/124$, $J = 30$ Hz (Figure 1, IV), which we ascribe to complex **K4**. The spectrum clearly shows that C–H activation yields a single compound in the case of the dbcot complex. Removal of the excess of *n*PrNH$_2$ did not effect reversal of C–H activation. However, addition of acetic acid led to clean transformation of **K4** into **K3** (see the Supporting Information).

Analogous to solution A, solution B contained 0.5 equiv [{Ir(dbcot)Cl}$_2$]. In order to avoid the presence of this compound, C–H activation was carried out with [{Ir(dbcot)Cl}$_2$]/**L2** (1:4). This procedure allowed very clean ^{1}H NMR spectra to be obtained; **K4** was characterized by ^{1}H NMR (COSY) and ^{13}C NMR spectroscopy (HMQC, DEPT) as well as by FAB$^+$ mass spectrometry.

These experiments demonstrate that the Ir complexes based on **L2** and dbcot are formed with high selectivity and are more stable to reversal of C–H activation than those of cod.

In conclusion, we have developed a new phosphoramidite iridium catalyst. In allylic substitutions, the new catalyst led to an unprecedented level of regioselectivity and made it possible for the first time to run the reactions in the presence of oxygen. In addition, we have for the first time demonstrated the reversiblity of the cyclometalation for phosphoramidite iridium complexes.

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[13] Crystal data for **K1**: See the Supporting Information.

[14] The ^{31}P NMR spectrum was measured at −60 °C in order to obtain sharp doublets for the minor diastereomer at $\delta = 152/142$ ppm. At RT the ^{31}P NMR spectrum showed a broadened signal for the doublet at 142 ppm.

[15] Hartwig et al. found doublets at $\delta = 152.6$ and 127.8 ppm, $^{3}J = 46$ Hz (94 %) and $\delta = 149.4$ and 146.0 ppm, $^{3}J = 78$ Hz (6 %) for diastereomers of type **K2** derived from **L1**, cf. Ref. [11].