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Enantioselective Iridium-Catalyzed Allylic Arylation

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Abstract: We describe herein the development of the first iridium-catalyzed allylic substitution using arylzinc nucleophiles. High enantioselectivities were obtained from the reactions, which used commercially available Grignard reagents as the starting materials. This methodology was also shown to be compatible with halogen/metal exchange reactions. Its synthetic potential is demonstrated by its application towards the formal synthesis of (+)-sertraline.

Keywords: allylic substitution · asymmetric catalysis · chiral ligands · cross-coupling · iridium

Introduction

The past several years have witnessed the development of a large number of new asymmetric catalytic reactions. Our group has contributed to this field and has studied, among others, the copper-catalyzed allylic substitution reaction.[1] In this reaction, palladium certainly stands as the most extensively studied catalytic system.[2] Palladium, when associated with chiral ligands, allows the allylation of the so-called soft or stabilized nucleophiles ($pK_a < 25$) with high stereocontrol and impressive turnover numbers. Despite notable efforts, the use of hard nucleophiles ($pK_a > 25$) with palladium catalysts has given rather limited results,[3] forcing research groups to turn their attention to other metals, such as copper. Since the pioneering work of Bäckvall and co-workers in 1995,[4] this metal has been used to catalytically transfer alkyl Grignard,[4,5] zinc,[6] and more recently aluminium[7] reagents with high regio- and enantioselectivities (Scheme 1). The copper system, however, could not be successfully extended to aryl nucleophiles[2b,8] and despite the work of many research groups using Co,[9] Ni,[10] Ti,[11] Pd,[12] Rh,[13] or Cu[14] catalysts, there is still no general and efficient system for such a transformation of prochiral allylic compounds. A regio- and stereospecific version, with an enantiopure chiral allylic fluorinated carbonate as the substrate, has been described by Evans.[15] Inspired by this work, our group recently developed a general and efficient iridium-catalyzed enantioselective allylic arylation reaction with moderate regioselectivity and good to high enantiocontrol.[16]

We present herein a full account of the development of this new methodology that has potential in the synthesis of a number of biologically active compounds (Scheme 2), as demonstrated by its utilization towards the formal synthesis of (+)-sertraline.

Results and Discussion

Thanks to the seminal achievements of the groups of Takeuchi,[20] Helmchen,[21] and Hartwig,[22] iridium is now being employed with a large range of nucleophiles in the allylic substitution reaction.[23] The γ-selectivity of iridium allows the transfer of stabilized nucleophiles, although more borderline nucleophiles have been successfully used, namely, ketone enolates,[24a] enamines,[24b] and silanolates.[25] Following this trend, we started testing hard nucleophiles with the iridium catalyst [{IrCl(cod)}$_2$] (cod = cycloocta-l,5-diene) and began our preliminary studies (Table 1) with ligand **L1**, which generally affords high regio- and enantioselectivities in both the Cu- and Ir-catalyzed allylic substitution.[1b,26]

At room temperature, the reaction carried out with four equivalents of PhMgBr led, unsurprisingly, to the full deprotection of substrate **1a** (Table 1, entry 1). The use of four equivalents of PhZnBr, formed in situ, resulted in the desired product with a promising enantiomeric excess (*ee*) of **2a**, although the reaction was sluggish and the yield low

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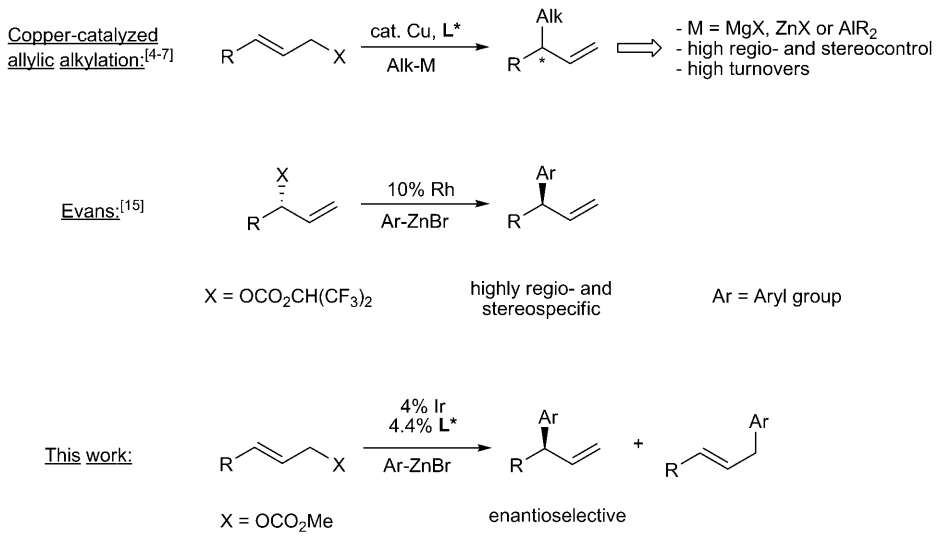
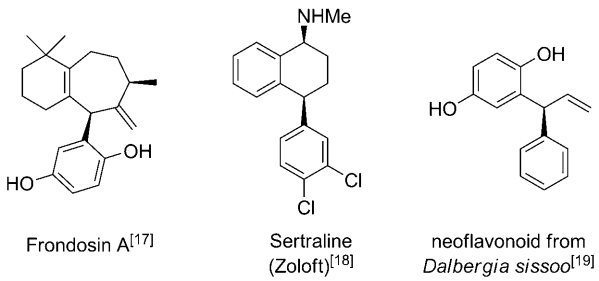


Scheme 1. Examples of allylic substitution reactions using nonstabilized nucleophiles.



Scheme 2. Natural and non-natural biologically active compounds that could arise from the asymmetric allylic transfer of an aryl group.

(Table 1, entry 2). The use of lithium halides as additives in the reaction (Table 1, entries 3–5) led to the complete conversion of compound **1a** into mixtures of **2a** and **3a**. Lithium bromide (Table 1, entry 4) was seen to give the best results (a point previously observed by the Evans group[15]); the reaction being both regio- (**2a**/**3a** > 2:1) and enantioselective (74%). The substitution reaction was also found to proceed under the more economical conditions in which 1.5 equivalents of the Grignard reagent, 0.75 equivalents of $ZnBr_2$, and 1.5 equivalents of LiBr, compared to that of the substrate **1a**, were used (Table 1, entry 6). The ratio of $ZnBr_2$ to the additive was found to be of importance; a ratio of 2:1 in favor of the additive led to a lower conversion (Table 1, entry 7) than that observed when the additive was in equal or greater equivalents (Table 1, entries 4 and 6). Finally, the reactions in which commercially available PhLi was used as the metal reagent gave decreased conversions of **1a** along with low regioselectivities and yields, both with (Table 1, entry 8) and without an additive (entry 9).[27] From the reactions summarized in Table 1, it was concluded that the best conditions for further studies were those used in entry 6.

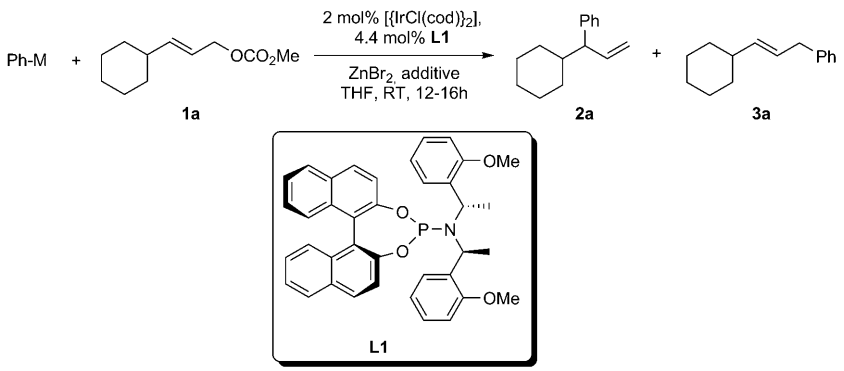
Having found the optimal conditions for the allylic substitution of **1a**, we studied the behavior of different leaving groups in the substitution reaction (Table 2). The carbonate derivative **1a** (Table 2, entry 1), although kinetically slower than the chloride derivative **1ab** (Table 2, entry 2), gave a better regioselectivity. The slightly less reactive, allylic acetate **1ac** (Table 2, entry 3) required heating to 40°C for the reaction to proceed, but did afford the best *ee*. In this case, however, the ratio of products **2a**/**3a** and the conversion of the reaction were lower than that for **1a**. Unfortunately, neither a phosphonate (**1ad**, Table 2, entry 4), nor a carbamate (**1ae**, Table 2, entry 5)[28] were able to improve the results obtained with **1a**. We therefore selected the carbonate leaving group for further studies as it is the best compromise between efficiency and reactivity.

Other solvents and organometallic species were tested (Table 3) in order to optimize the reaction. Diethyl ether (Table 3, entry 1) and dichloromethane (Table 3, entry 2) were not as attractive as THF for this reaction. It is interesting to observe that the chloride anion, when $ZnCl_2$ was used as the organometallic species (Table 3, entry 3) or when LiCl was used as the additive (Table 3, entry 4), was significantly detrimental to the reaction rate giving conversions lower than 10% in each case. Copper (Table 3, entry 5) and manganese (Table 3, entry 6) phenyl species were then tried as the organometallic reagent, but without any success. Another complex of iridium, $[Ir(cod)_2]BF_4$, with more cationic character (Table 3, entry 7) also led to inferior performances. Co-solvents, such as *N*,*N*′-dimethyl-*N*,*N*′-propylene urea (DMPU), *N*,*N*-dimethylacetamide (DMA), and 1,4-diazabicyclo[2.2.2]octane (DABCO), or the slow addition of the diphenylzinc species did not improve the results.[29]

We then screened different types of ligands (Scheme 3 and Table 4) to determine which was the most effective for our system. Interestingly, the iridium complex devoid of any ligand gave a satisfactory, selective conversion of **1a** to the linear isomer **3a** (Table 4, entry 1). The screening of various nonchiral phosphorus ligands (Table 4, entries 2–5) led to the observation that unlike the initial studies by Takeuchi,[20] the regioselectivity of the reaction is independent of the electron-withdrawing properties of the ligand, a phenomenon recently noticed by Nomura.[30]

Of all the chiral ligands tested, none were found to give better regioselectivity than **L1**, however, some, such as **L8** (Table 4, entry 13), **L9** (Table 4, entry 14) and **L16** (Table 4, entry 19), led to better enantioselectivities. Although **L8** and **L9** were rather disappointing in terms of regioselectivity, the

Table 1. Preliminary studies with ligand **L1** and substrate **1a**.[a]



Entry	M (equiv)	$ZnBr_2$ (equiv)	Additive (equiv)	**2a**/**3a**[b]	Conv. [%][b] (Yield [%])	*ee* [%][c]
1	MgBr (4)	–	–	–	100[d]	–
2	MgBr (4)	4	–	53:47	34	58
3	MgBr (4)	4	LiCl (4)	61:39	100	73
4	MgBr (4)	4	LiBr (4)	69:31	100	74
5	MgBr (4)	4	LiI (4)	60:40	100	74
6	MgBr (1.5)	0.75	LiBr (1.5)	66:34	100 (72)	75
7	MgBr (1.5)	3	LiBr (1.5)	55:45	54	74
8	Li (1.2)	1.2	LiBr (1.2)	33:67	43	57
9	Li (1.2)	1.2	–	45:55	52	75

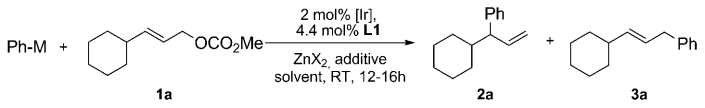
[a] Each reaction was carried out on a 0.5 mmol scale of substrate in THF (2.5 mL) for 15–18 h before hydrolysis (see the Experimental Section). [b] Ratio of **2a**/**3a** and conversion measured by GC–MS or ^{1}H NMR spectroscopy. Yield combining **2a** and **3a**. Isolated yield in parentheses. [c] Measured by chiral GC. [d] Recovery of the allylic alcohol.

Table 2. Evaluation of different leaving groups.[a]

Entry	X, Substrate	*T* [°C]	*t* [h]	**2a**/**3a**[b]	Conv. [%][b]	*ee* [%][c]
1	OCO_2Me, **1a**	25	16	66:34	100	75
2	Cl, **1ab**	25	2	52:48	100	71
3	OAc, **1ac**	40	40	61:39	86	82
4	$OPO(OEt)_2$, **1ad**	25	28[d]	44:56	100	68
5	OCONHPh, **1ae**	25	20	25:75	21	n.d.[e]

[a] Each reaction was carried out on a 0.5 mmol scale of substrate using the optimal conditions (Table 1, entry 6) and kept at the indicated temperature. [b] Measured by GC–MS or ^{1}H NMR spectroscopy. [c] Measured by chiral GC. [d] Reaction time not optimized. [e] Not determined.

Table 3. Variation of solvents, anions, organometallic species, and iridium source.[a]



Entry	M (equiv)	ZnX_2 (equiv)	Additive (equiv)	Solvent	**2a**/**3a**[b]	Conv. [%][b]	*ee* [%][c]
1	MgBr (1.5)	$ZnBr_2$ (0.75)	LiBr (1.5)	Et_2O	56:44	83	55
2	MgBr (1.5)	$ZnBr_2$ (0.75)	LiBr (1.5)	CH_2Cl_2	59:41	63	6
3	MgBr (1.5)	$ZnCl_2$ (0.75)	LiBr (1.5)	THF	29:71	5	64
4	MgCl (1.5)	$ZnCl_2$ 0.75	LiCl (1.5)	THF	24:76	7	n.d.[d]
5	MgBr (1.5)	CuBr (1.5)	LiBr (1.5)	THF	61:39	100	24
6	MgBr (1.5)	$MnCl_2$ (1.5)	LiCl (1.5)	THF	22:78	16	66
7[e]	MgBr (1.5)	$ZnBr_2$ (0.75)	LiBr (1.5)	THF	50:50	45	71

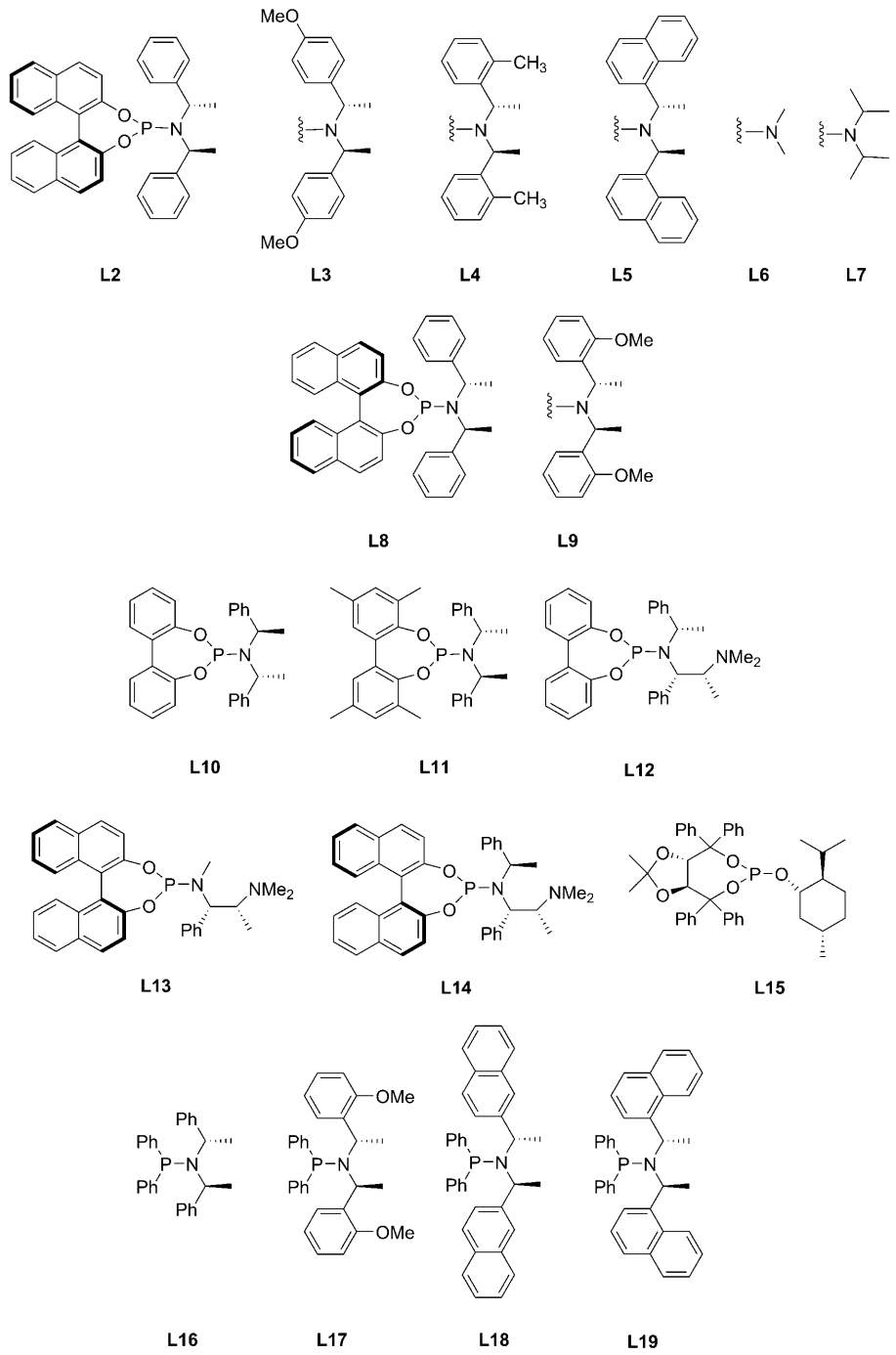
[a] Each reaction was carried out on a 0.5 mmol scale of **1a** in the indicated solvent using the optimal conditions (Table 1, entry 6). [b] Measured by GC–MS or ^{1}H NMR spectroscopy. [c] Measured by chiral GC. [d] Not determined. [e] Source of iridium: $[Ir(cod)_2]BF_4$.

performance of our newly described Simplephos **L16**[31] (Table 4, entry 19) was very close to that of **L1**.

Considering the results obtained for **L2** (Table 4, entry 7),[32] the methoxy substituents of other ligands seem to play an important role in obtaining higher regio- and enantioselectivities.[33] Similarly, the position and the nature of the substituents on the amino part of the ligand are crucial: **L3** (Table 4, entry 8) with the methoxy group in the *para* position or **L4** (Table 4, entry 9) with methyl groups in the *ortho* position gave rise to lower enantio- and regioselectivities. These results suggest that in **L1**, the methoxy groups might play a coordinating role; a situation totally different to our observations with stabilized nucleophiles[33] and one in which deeper investigation needs to be performed to comment any further.

Other ligands with either larger (Table 4, entry 10) or smaller (Table 4, entries 11–12) amino moieties did not improve the results. In the worst cases, ligands such as the ferrocenyl-based Josiphos (Josiphos = 1-[2-(diphenylphosphanyl)ferrocenyl]ethyldicyclohexylphosphane) and Taniaphos (Taniaphos = 1-(*S*)-diphenylphosphanyl-2-(*O*-diphenylphosphanylphenylmethyl)ferrocene), as well as Binap (Binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene) gave less than 10% conversion.

An interesting outcome was obtained when ligands **L8** and **L9**, diastereomers of **L2** and **L1**, respectively, were used (Table 4, entries 13–14). In **L8** and **L9** the binapthol moiety has the *aR* configuration and the amine the *S*,*S* configuration, whereas in **L2** and **L1** the binapthol has the *aS* and the amine the *S*,*S* configuration. Both **L8** and **L9** generated a significant increase in enantioselectivity (80 and 84%, respectively) compared with **L2** (66%) and **L1** (75%), although these ligands preferentially gave the linear adduct (13:87 and 30:70 respectively). Biphenol-type ligands, such as **L10** and **L11**, also gave a larger proportion of the linear isomer (Table 4, entries 15–16).



Scheme 3. Chiral ligands used in this study.

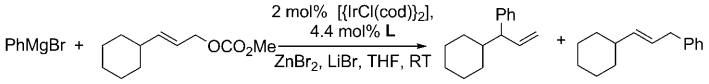
Low conversions of **1a** were obtained when testing ligands such as the ephedrine- or the α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL)-based families (Table 4, entries 17–18). On the other hand, the newly described "Simplephos" family of ligands[31] (Table 4, entries 19–21) and particularly **L16** (Table 4, entry 19) led to good enantioselectivities together with acceptable regioisomeric ratios, although **L1** was still seen to give the best results and will be used as the ligand of choice for further studies.

Having the optimal ligand and reaction conditions in hand, we turned our attention to different substrates. We were particularly keen on testing 3-arylprop-2-en-1-ol derivatives because the corresponding products, 3,3-diarylprop-1-enes, represent useful entries to optically enriched α,α-diaryl products. For this study, we changed both the steric and electronic properties of the aryl groups (Table 5).

At first glance of the various substrates used, the reaction scope seems to be quite general. High enantioselectivities (>90%) are usually obtained, with one example above 99% (Table 5, entry 5). Also, the regioselectivity usually stands slightly above 50%, an unprecedented level for this type of reaction. The most striking observation could be made from entries 1 and 9 in which a heteroatom is present in the *ortho* position of the substrate (Table 5, entry 1, *ortho*-OMe-phenyl; entry 9, *ortho*-furanyl). In both cases the position of the substituent seemed to have a detrimental impact on the enantioselectivity of the reaction (78 and 79% *ee*, respectively). Low enantioselectivity was also observed when using other kinds of nucleophiles, such as amines[22] or malonates.[26] When the heteroatom was in a different position of the substrate, either in the *meta* (Table 5, entry 2) or *para* (Table 5, entry 3) positions, high enantioselectivities were obtained (90 and 91% respectively). We could not, however, rationalize the unfavorable regioselectivity observed in the case of the *para*-OMe substituent (Table 5, entry 3).

The varying of the substituents of the substrates, with regards to their electron withdrawing properties, was also undertaken with no marked effect being observed (compare entries 3–7). Entry 11 highlights the limitations of this new methodology; when the substituent on the allylic carbonate

Table 4. Comparison of different chiral and nonchiral ligands.[a]

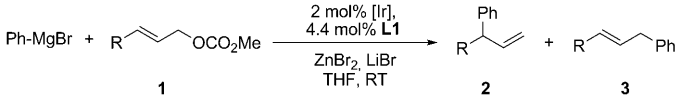


1a 2a 3a

Entry	L	2a/3a[b]	Conv. [%][b] (*ee* [%])[c]	Entry	L	2a/3a[b]	Conv. [%][b] (*ee* [%])[c]
1	–	5:95	89 (–)	12	**L7**	40:60	79 (35)
2	PPh_3	20:80	42 (–)	13	**L8**	13:87	96 (80)
3	$P(NMe_2)_3$	31:69	38 (–)	14	**L9**	30:70	100 (84)
4	PBu_3	5:95	89 (–)	15	**L10**	18:82	85 (−74)
5	$P(OEt)_3$	6:94	89 (–)	16	**L11**	16:84	97 (71)
6	**L1**	66:34	72[d] (75)	17	**L12**	48:52	28 (−15)
7	**L2**	47:53	98 (66)	18	**L13**	40:60	3 (n.d.[e])
8	**L3**	50:50	96 (64)	19	**L14**	59:41	88[d] (83)
9	**L4**	39:61	100 (64)	20	**L15**	40:60	71 (55)
10	**L5**	34:66	99 (71)	21	**L16**	58:42	88 (73)
11	**L6**	9:91	71 (2)				

[a] All experiments were run on a 0.5 mmol scale of **1a** in THF (2.5 mL) according to the optimal conditions (Table 1, entry 6). Reaction time: 16–20 h. [b] Measured by GC–MS or ^{1}H NMR spectroscopy. [c] Measured by chiral GC. [d] Yield obtained after column chromatography on SiO_2. [e] Not determined.

Table 5. Investigation into the scope of the substrates.[a]



1 2 3

Entry	1	R	L1	Product	2/3[b]	Conv. [%][b] (Yield [%])[c]	*ee* [%][d]
1	**1b**	*o*-MeO-C_6H_4	(*aR*,*RR*)	**2b**	42:58	100	78 (*S*)
2	**1c**	*m*-MeO-C_6H_4	(*aR*,*RR*)	**2c**	49:51	100 (67)	90 (*S*)
3	**1d**	*p*-MeO-C_6H_4	(*aS*,*SS*)	**2d**	33:67	100 (78)	91 (*R*)
4	**1e**	*p*-F-C_6H_4	(*aS*,*SS*)	**2e**	50:50	100 (83)	93 (*R*)
5	**1f**	*p*-Cl-C_6H_4	(*aR*,*RR*)	**2f**	55:45	100 (83)	99.2 (*S*)
6	**1g**	3,4-Cl_2-C_6H_3	(*aS*,*SS*)	**2g**	57:43	100 (89)	95 (*R*)
7	**1h**	*p*-CF_3-C_6H_4	(*aR*,*RR*)	**2h**	56:44	100 (98)	97 (*S*)
9	**1i**	2-furyl	(*aR*,*RR*)	**2i**	73:27	100	79 (*S*)
10	**1j**	2-naphthyl	(*aS*,*SS*)	**2j**	53:47	100 (93)	92 (*R*)
11[e]	**1k**	*n*Pr	(*aS*,*SS*)	**2k**	54:46	100	15 (n.d.[f])

[a] All experiments were run on a 0.5 mmol scale of **1** in THF (2.5 mL) according to the optimal conditions (Table 1, entry 6); Reaction time: 16–20 h. [b] Measured by GC–MS or ^{1}H NMR spectroscopy. [c] Yield determined by ^{1}H NMR spectroscopy. [d] Measured by chiral GC. [e] Four equivalents of PhMgBr, $ZnBr_2$, and LiBr were used (reaction $t = 120$ h, not optimized). [f] Not determined.

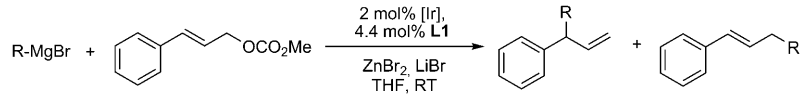
was a linear aliphatic chain, such as an *n*-propyl group, the enantioselectivity of the reaction dropped dramatically.

After investigating the scope and limitations of the substrates, we tested several commercially available Grignard reagents for their nucleophilic properties (Table 6). The selected Grignard reagents were treated with zinc bromide and lithium bromide according to the usual procedure (see Table 1 and the Experimental Section). In general, the species with aryl substituents gave results similar to those obtained when R = Ph with enantioselectivities in the range 80–91% together with acceptable regioisomeric selectivity of the desired adducts (Table 6, entries 1, 2, 4 and 5). The only notable exception concerns the 3,4-dichlorophenyl derivative (Table 6, entry 3), which gave reduced regio- and enantioselectivities. Alkyl Grignard reagents, such as MeMgBr, did not fit well into this type of system (Table 6, entry 6) and it has been previously noted that copper is the best catalyst for these reagents.[34]

The availability of functionalized Grignard reagents in the laboratory has been extensively demonstrated by Knochel.[35] After testing commercially available organomagnesium nucleophiles, we became interested in implementing our methodology by combining the halogen/metal exchange reaction (I/Mg or I/Li)[35] and our allylic substitution reaction. The results obtained for selected examples are presented in Table 7. We were pleased to observe that the I/Mg exchange procedure, followed by transmetallation with $ZnBr_2$ and allylic substitution using our standard aliphatic substrate **1a** (Table 7, entry 1), gave almost identical results as with the commercially available PhMgBr reagent (Table 1, entry 6). This was not the case, however, for the aromatic substrates used in this study. For example, the *p*-MeO-phenyl substituent gave a disappointing outcome with significantly lower selectivities (Table 7, entry 2). We then compared the I/Mg and I/Li exchange procedures on the same aromatic pronucleophile, *p*-F-phenyl (Table 7, entries 3 and 4). From these two experiments, we were able to conclude that the I/Li exchange reaction (Table 7, entry 4) gave similar regioselectivities, but higher enantioselectivities than the I/Mg procedure (Table 7, entry 3). The experiments shown in entries 1–3 are among the first examples of the use of the Knochel's exchange methodology in asymmetric catalysis. The Br/Li exchange was also investigated with the 2-bromonaphthalene-substituted compound in which slightly lower enantio- and regioisomeric yields than the commercially available 2-MgBr-naphthalene were obtained (Table 7, entry 5).

The absolute configurations of adducts **2** were determined by comparison of the rotation of **2a** with known literature data.[36] We then decided to apply our methodology to the total synthesis of a known intermediate in the preparation of (+)-sertraline, a serotonin uptake inhibitor used in the treatment of depression (Scheme 4).[18,37] Compound **2g** was

Table 6. Investigations into the scope of the nucleophiles.[a]

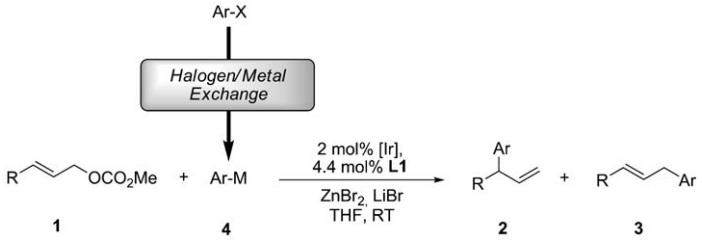


4 1l 2 3

Entry	L1	4	R	2	2/3[b]	Conv. [%][b] (Yield [%])[c]	*ee* [%][d]
1	(*aS*,*SS*)	**4d**	*p*-MeO-C_6H_4	**2d**	57:43	100 (98)	91 (*S*)
2	(*aS*,*SS*)	**4e**	*p*-F-C_6H_4	**2e**	45:55	100 (95)	82 (*S*)
3	(*aR*,*RR*)	**4g**	3,4-Cl_2-C_6H_4	**2g**	16:84	100 (98)	63 (*R*)
4	(*aS*,*SS*)	**4h**	*p*-CF_3-C_6H_4	**2h**	40:60	100 (78)	80 (*S*)
5	(*aS*,*SS*)	**4j**	2-naphthyl	**2j**	63:37	100 (97)	91 (*S*)
6	(*aS*,*SS*)	**4l**	Me	**2l**	18:82	100	6 (*S*)

[a] All experiments were run on a 0.5 mmol scale of **1l** in THF (2.5 mL) according to the optimal conditions (Table 1, entry 6); Reaction time: 16–20 h. [b] Measured by GC–MS or ^{1}H NMR spectroscopy. [c] Yield determined by ^{1}H NMR spectroscopy. [d] Measured by chiral GC.

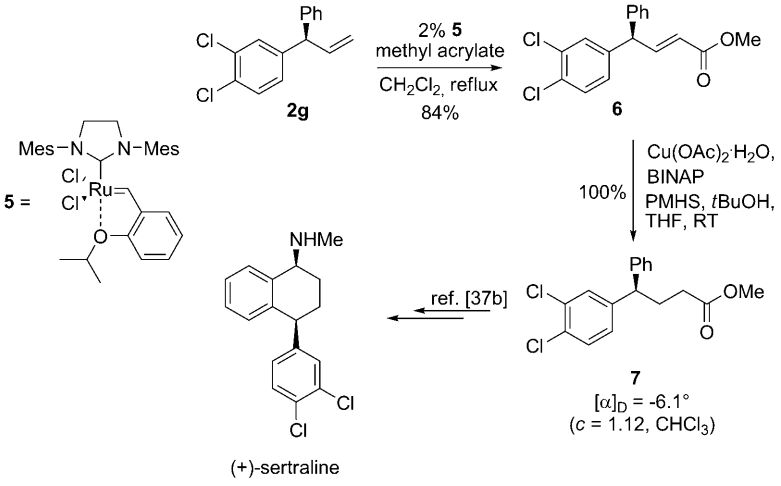
Table 7. Nucleophiles obtained by halogen/metal exchange.[a]



1 4 2 3

Entry	Substrate	R	L1	Method[b]	Ar	Product	2/3[c]	Conv. [%][c] Yield [%][d]	*ee* [%][e]
1	**1a**	*c*-hex	(*aS*,*SS*)	A	Ph	**2a**	54:46	100 (72)	77 (*S*)
2	**1d**	*p*-MeO-C_6H_4	(*aS*,*SS*)	A	Ph	**2d**	18:82	100 (65)	44 (*R*)
3	**1e**	*p*-F-C_6H_4	(*aS*,*SS*)	A	Ph	**2e**	46:54	100 (87)	78 (*R*)
4	**1e**	*p*-F-C_6H_4	(*aS*,*SS*)	B	Ph	**2e**	44:56	100 (53)	87 (*R*)
5	**1l**	Ph	(*aS*,*SS*)	B	2-naphthyl[f]	**2j**	40:60	100 (78)	80 (*S*)

[a] All experiments were run on a 0.5 mmol scale of **1l** in THF (2.5 mL) according to the optimal conditions (Table 1, entry 6); Reaction time: 16–20 h. [b] Method A: I/Mg exchange; Method B: I/Li exchange. [c] Measured by GC–MS or ^{1}H NMR spectroscopy. [d] Yield determined by ^{1}H NMR spectroscopy. [e] Measured by chiral GC. [f] Br/Li exchange.



Scheme 4. Towards the enantioselective formal synthesis of (+)-sertraline.

submitted to cross-metathesis conditions with methyl acrylate and the Hoveyda–Grubbs catalyst **5**.[38] The double bond of the resulting unsaturated ester **6** was then reduced under mild conditions by using a copper-catalyzed 1,4-reduction reaction[39] leading to ester **7**, a known intermediate in Davies' synthetic approach to sertraline.[37b]

Compared to stabilized nucleophiles, such as malonates and amines, the arylzinc nucleophiles studied in this work give rise to the same facial selectivity.[27] This observation is quite intriguing given the inherent difference between the two nucleophilic species. One could possibly envisage the following hypotheses, among others (Figure 1): 1) The nature of the iridium(I) catalyst is that of the commonly accepted one;[23b] the oxidative addition of the iridium catalyst occurs on the usual side (*Re* if R = cyclohexyl), which is followed by an *anti* attack of the aryl nucleophile. 2) The selected conditions generate a different iridium(I) catalyst, already containing the aryl group; the oxidative addition takes place on the opposite side (*Si* if R = cyclohexyl), which is followed by a reductive elimination process on the same side. It can also be speculated whether the branched and linear regioisomers arise from the same reaction intermediate or from two different pathways: the branched product following pathway A, whereas the linear product could arise from pathway B.

Next, we tried our methodology on acetate **8** under kinetic resolution conditions with 0.55 equivalents of Ph_2Zn (Scheme 5). After the reaction was stirred for two hours, at 51% conversion, the ratio of adducts **2a** to **3a** (4:1) was much greater than that found

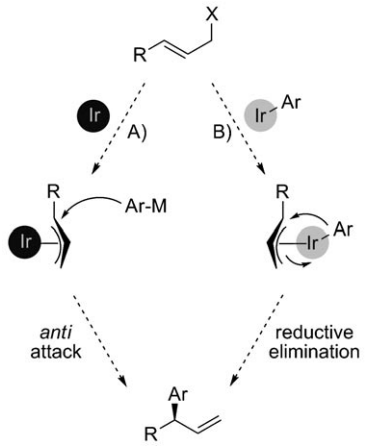


Figure 1. Two possible pathways explaining the product stereochemistry; A) *anti* attack pathway and B) reductive elimination pathway.

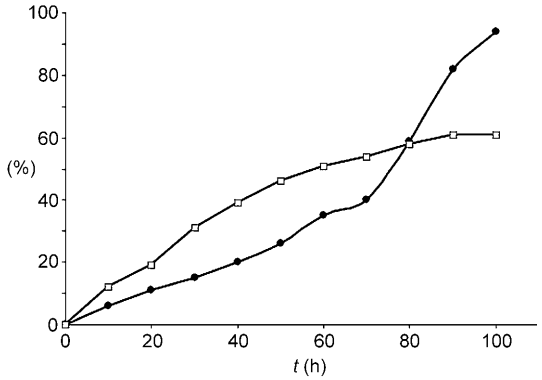


Figure 2. Evolution of the regioisomeric proportion **2a**/**3a** relative to **2a** under the usual conditions (Table 1, entry 6). ●: conversion, □: regiomeric proportion.

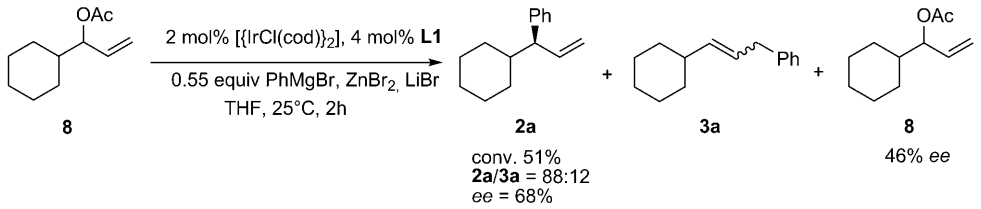
when starting from **1a** (2:1). The enantiomeric excess of **2a**, in the case of the acetate, was 68%. In addition, the reaction was much faster than with **1a**.[23b] This experiment shows that the regiospecificity of the catalyst is of much greater importance in the case of nonstabilized nucleophiles. On the other hand, the selectivity factor ($s=4$)[40] remained close to that obtained with stabilized nucleophiles, such as malonates[27].

Concerning the standard reaction (Table 1, entry 6), the evolution of the regioisomeric ratio over time was followed by gas chromatography (Figure 2). We were surprised to observe that the desired isomer represents a minor fraction of the products up to around 35% conversion and gradually increases over time to eventually become the major regioisomer at the end of the reaction. This observation could make one suppose that a chemical species is probably accumulating as the reaction progresses enabling the formation of the desired isomer, however, all attempts to investigate the reasons for the regioisomeric evolution were unfruitful. These attempts involved running the reaction in the presence of a stoichiometric or catalytic amount of adduct **2a**, or to introduce either MeOLi or AcOLi as additives, but none of these perturbations led to an improvement of the regioisomeric yield. Similarly, adding another equivalent of the starting material **1a** and the arylzinc species to the reaction mixture after full conversion of the first equivalent was no more successful. Although deeper investigation is needed to draw any further conclusions, we suppose that more than one catalytic species are present in the reaction mixture.

Since the mechanistic aspects of this reaction seemed somewhat different from the classical malonate substitution, we tested some previously unreactive allylic substrates. Thus, we tried our methodology on cyclic substrates such as *rac*-**9**. In Pd chemistry, such substrates are *meso*-π-allyl and can be desymmetrized by the incoming nucleophile.[3] We wondered if this would also be the case with Ir-catalyzed arylation because this would remove the linear/branched problem. For this study, three substrates were tested: the carbonate **9a**, the acetate **9b**, and the bromide **9c** (Table 8). The arylation of such substrates had already been examined with various transition-metal complexes, excluding iridium, with good to excellent results.[10e,12a,41]

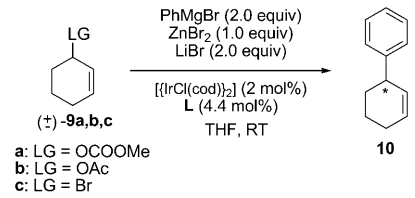
Carbonate **9a** reacted readily and cleanly under our standard conditions to afford compound **10**. In contrast, we were never able to obtain any adducts using stabilized nucleophiles (such as malonates), even under forced conditions (reflux temperature).[27] In this case, **L1** is not an efficient ligand (Table 8, entry 1). Among the usual phosphoramidite ligands, **L10** gave the best result with 76% *ee* (Table 8, entry 4). Ligand **L14**, which has an extra nitrogen on the amine part of the ligand, gave a similar result, particularly when 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TDB)[42] was added as cocatalyst (Table 8, entry 5). When PhZnBr/$MgBr_2$ was used, the *ee* could be improved to 82% (Table 8, entry 6).

Acetate **9b** was clearly the least reactive of these substrates. Often the conversions were not quantitative, howev-



Scheme 5. Allylic arylation under kinetic resolution conditions.

Table 8. Arylation of **9**.[a]



Entry	Substrate	L	Additive ([%])	Conv. [%][b] (Yield [%])[c]	*ee* [%][d]
1	**9a**	**L1** (a*S*,SS)	–	96	15 (*S*)
2	**9a**	**L11** (a*S*,*SS*)	–	100	35 (*S*)
3	**9a**	**L12** (a*S*,*SS*)	–	100	60 (*S*)
4	**9a**	*ent*-**L10** (*SS*)	–	100	76 (*S*)
5	**9a**	**L14**	TDB (8)	97	74 (*R*)
6	**9a**	**L14** $PhZnBr/MgBr_2$	TDB (8)	100	82 (*R*)
7	**9b**	**L1** (a*S*,*SS*)	–	98	43 (*S*)
8	**9b**	**L2** (a*S*,*SS*)	–	76	57 (*S*)
9	**9b**	**L8** (a*R*,*SS*)	–	15	46 (*S*)
10	**9b**	**L12**	–	91	45 (*S*)
11	**9b**	**L12**	TDB (8)	82	79 (*S*)
12	**9b**	**L11** (*SS*)	–	77	84 (*R*)
13	**9b**	*ent*-**L10** (*SS*)	–	83	88 (*S*)
14	**9b**	*ent*-**L10** (*SS*)	TDB (8)	96	84 (*S*)
15	**9b**	**L14**	TDB (8)	85 (79)	90 (*R*)
16	**9c**	**L1** (a*S*,*SS*)	–	100	54 (*S*)
17	**9c**	**L1** (a*S*,*SS*) $PhZnBr/MgBr_2$	–	99	63 (*S*)
18[e]	**9c**	**L1** (a*S*,*SS*) $PhZnBr/MgBr_2$	–	98	75 (*S*)
19	**9c**	*ent*-**L10** (*SS*)	–	97	84 (*S*)
20	**9c**	*ent*-**L10** (*SS*) $PhZnBr/MgBr_2$	–	100	55 (*S*)

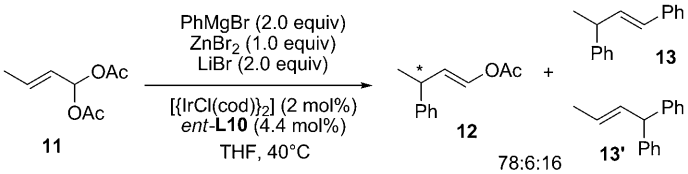
[a] All experiments were run on a 0.5 mmol scale of **9** in THF (2.5 mL) according to the optimal conditions (Table 1, entry 6); Reaction time: 16–20 h. [b] Measured by GC–MS or ^{1}H NMR. [c] Yield determined by ^{1}H NMR spectroscopy. [d] Measured by chiral GC. [e] Reaction run at 0 °C.

er, some of the best enantioselectivities were achieved with this substrate. Again, **L1** was not the best choice of ligands. A match/mismatch situation could be seen with **L2** and **L8** (Table 8, entries 8 and 9), affecting, not the enantioselectivities, but the conversion. As was seen for carbonate **9a**, ligand **L10** gave excellent results with **9b** (Table 8, entry 14; 84% *ee*), although the addition of TDB showed no improvement. Finally, the best selectivities were found with **L14** and TBD with 90% *ee* obtained (Table 8, entry 15).

The bromide **9c** was the most reactive substrate. Even without the catalyst present, the reaction proceeded at a significant rate, with $Ph_2Zn/MgBr_2$ (the reaction was over in 10 min at room temperature). Using $PhZnBr/MgBr_2$ as the reagent allowed a slower background reaction. In the case of **9c**, **L1** was more successful than for the other substrates. The 54% *ee* (Table 8, entry 16) could be improved to 63% with $PhZnBr/MgBr_2$ (Table 8, entry 17), and even to 75% at 0 °C (Table 8, entry 18). Here again, ligand **L10** appeared to be the best ligand with 84% *ee* (Table 8, entry 19).

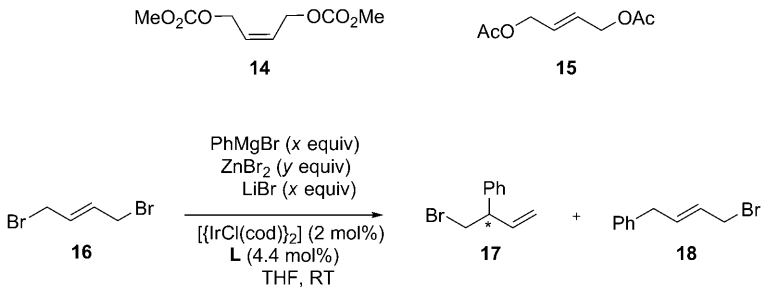
Difunctional substrates are also of interest. For example, the easily prepared diacetate **11** (Scheme 6), has previously been used by Trost and Lee with stabilized nucleophiles.[43] With a Pd-based catalyst, only the α (linear) product is obtained, giving rise to an enantioenriched allylic acetate. In contrast, with Ir-based catalysts, we expected the γ (branched) product, which formally corresponds to a conjugate addition to the parent aldehyde. Although the malonate-type nucleophiles did not react with under Ir catalysis conditions, we did observe a reaction with $Ph_2Zn/MgBr_2$ (Scheme 6). The reaction gave the expected branched isomer **12**, along with two other products, **13** and **13′**, in a 78:6:16 ratio. Products **13** and **13′** arise from the linear allylic acetate, followed by a second allylic substitution, both from α and γ attack. The *ee* value of **12** was only 29%, and no further studies were done on this substrate.

We instead focused on 1,4-difunctionalized allylic substrates. For example, the *Z* dicarbonate **14** was unreactive with malonates under Ir catalysis conditions. In the arylation reaction (Scheme 7), it gave mostly the linear product (yield = 90%, branched/linear = 7:93), although this was predictable because Helmchen and co-workers demonstrated the different



Scheme 6. Allylic arylation on a *gem*-difunctionalized substrate.

behavior of *E* and *Z* isomers.[44] The *E* diacetate **15**, prepared from the dibromide **16**,[45] gave only 25% of racemic linear isomer. Finally, we turned our attention to the *E* dibromide **16**, which is commercially available and has previously been exploited in Cu-catalyzed allylic substitution.[46] Interestingly, in Cu-catalyzed reactions, compound *E*-**16** gave 100% branched product, probably due to a favorable interaction between the bromide and the copper reagent. The first experiment with **L1** showed, as expected, a moderate preference for the branched product. Compared with carbonates or acetates, however, the bromides are much more reactive (Table 9) and part of the reaction outcome was as a result of an uncatalyzed background reaction. Indeed, the Grignard reagent itself was quite reactive, but barely regioselective (Table 9, entry 1). Turning to the less reactive $PhZnBr/MgBr_2$ was more rewarding (Scheme 7 and



Scheme 7. Allylic arylation on a difunctionalized allylic substrate.

Table 9), both for the regioselectivity and the enantioselectivity (compare Table 9, entries 2 and 3).

Table 9. Arylation of dibromide **16**.[a]

Entry	PhMgBr (equiv)	$ZnBr_2$ (equiv)	L	Ratio[b] **17**/**18**	Conv.[%][c] (Yield[%])[b]	*ee* [%][d]
1	1.5	–	–	38:62	75	–
2	1.5	0.75	**L1** (*aR*,*RR*)	65:35	100	13 (*R*)
3	1.5	1.5	**L1** (*aR*,*RR*)	84:16	100	48 (*R*)
4[e]	1.5	1.5	**L1** (*aR*,*RR*)	97:3	100	65 (*R*)
5	2	1	**L8**	64:36	100	54 (*R*)
6	2	1	**L8** + TBD (8%)	98:2	100	76 (*R*)
7	1	1	**L8** + TBD (8%)	94:6	84	68 (*R*)
8[f]	2	1	**L8** + TBD (8%)	99:1	100 (85)	80 (*R*)
9	1.5	1.5	**L16** (*SS*)	77:23	100	60 (*S*)
10	1.5	1.5	**L17** (*SS*)	97:3	100	69 (*S*)
11	1.5	1.5	**L18** (*SS*)	71:29	100	21 (*S*)
12	1.5	1.5	**L19** (*SS*)	90:10	100	67 (*S*)

[a] All experiments were run on a 0.5 mmol scale of **14** in THF (2.5 mL) according to the optimal conditions (Table 1, entry 6); Reaction time: 16–20 h, except for entries 6, 7 and 8 (1 h). [b] Measured by GC–MS or ^{1}H NMR spectroscopy. [c] Yield determined by ^{1}H NMR spectroscopy. [d] Measured by chiral GC. [e] Reaction run at 0°C. [f] Reverse addition (substrate after nucleophile).

When using $PhZnBr/MgBr_2$, lowering the temperature of the reaction to 0°C (Table 9, entry 4) yielded the best results, both for regio- and enantioselectivity (97:3 and 65% *ee*). In contrast to previous results (Table 4), ligand **L8** appeared to be a good ligand, with respect to the obtained *ee* value (Table 9, entry 5). In accordance with the work of Helmchen and co-workers,[42] we observed that activation with TBD improved both the regio- and enantioselectivities (Table 9, compare entries 5 and 6). TBD activation of the catalyst was tested with several ligands, including **L1** and **L10**, but **L8** gave the best result. Finally, the addition of the nucleophile to the reaction mixture, followed by addition of the substrate (the reverse of above) led to our best result. In this case we obtained almost perfect regioselectivity (99:1) and very good enantioselectivity (80% *ee*) with **L8** (Table 9, entry 8). This is, presently, the best enantioselectivity achieved for the arylation of this substrate. Of particular interest were our new SimplePhos ligands.[31] Thus, ligand **L16** afforded 60% *ee* at room temperature. Among the other SimplePhos ligands (**L16**–**L19**), ligand **L17** gave the best results (97:3 and 69% *ee*, entry 10). It was particularly interesting to observe an inversion in the configuration of the branched adduct obtained with phosphoramidite ligand compared with the SimplePhos ligands.

Conclusion

We have developed an asymmetric allylic arylation reaction using iridium. Associated with phosphoramidite or aminophosphine (SimplePhos) ligands, iridium forms a very efficient catalyst for the transfer of arylzinc reagents. The desired branched adducts were obtained in moderate regioselectivities, but high enantioselectivities (up to 99% *ee*). The use of diarylzinc reagents, obtained from the corresponding Grignard reagents, were compatible with several halogen/metal exchange reactions.

We applied our methodology to the synthesis of useful diaryl alkenes and more particularly to an intermediate, which was used in the synthesis of (+)-sertraline. Future work aimed at improving the regioselectivities will be directed towards the understanding of the mechanism and the development of new chiral ligands.

Experimental Section

General methods: All reactions were carried out under argon atmosphere with oven-dried glassware. Solvents were dried by filtration over alumina (previously activated at 350°C over 12 h) under nitrogen before use. Solvents were degassed by the bubbling through of nitrogen prior to all experiments. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker 400F NMR in $CDCl_3$. Chemical shift values (δ) are given in ppm relative to residual $CHCl_3$. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), qd (quartet of doublet), brs (broad singlet). Coupling constants are reported in Hertz (Hz). The evolution of the reactions was followed by GC–MS (EI mode) on an HP6890 instrument. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at 20°C in a 10 cm cell in the stated solvent ; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentration *c* given as g/100 mL). Enantiomeric excesses were determined by two different methods. The first was by use of a chiral-SFC measurement on a Berger SFC with the stated column. Gradient programs are described as follows: initial methanol concentration (%)–initial time (min)–

percent gradient of methanol (% min^{-1})–final methanol concentration (%); retention times (t_R) are given in min. The second method was by chiral GC measurements either on a HP6890 (H_2 as vector gas) or HP6850 (H_2 as vector gas) instrument with the stated column. Temperature programs are described as follows: initial temperature (°C)–initial time (min)–temperature gradient (°C min^{-1})–final temperature (°C); retention times (t_R) are given in min. Flash chromatography was performed using silica gel 32–63 μm, 60 Å.

All chiral ligands were prepared according to the literature procedures (for ligands **L1**–**L11**, see references [26], [33], [47], and [48]; for ligands **L12**–**L15**, see references [49] and [50]; for ligands **L16**–**L19**, see reference [31]). Lithium bromide and lithium chloride were dried at 80°C over 24 h prior to use. [{IrCl(cod)}$_2$] was purchased from Strem and used as received. Allylic carbonates and acetates were synthesized by known experimental procedures.[51]

Typical procedure for allylic arylation of carbonates 1a–1k

Preparation of the nucleophilic solution: In a flame-dried flask containing dry THF (2 mL for each mmol of starting material), $ZnBr_2$ (0.75 equiv) and LiBr (1.5 equiv) were added (equivalents are relative to substrate). The solution was stirred for 10–15 min at room temperature. The corresponding solution of Grignard reagent (1.5 equiv) was then added to the flask. The resulting solution was ready to be used.

*Procedure for the Ir-catalyzed arylation of **1g***: A flame-dried Schlenk tube was charged with ligand **L1** (*S*,*SS*) (4.4%), [{IrCl(cod)Cl}$_2$] (2%), and dry THF (1 mL for each mmol of starting material). The resulting orange solution was stirred for 10–15 min at room temperature. The substrate **1g** (4 mmol) was then added and the reaction mixture was treated with the nucleophilic solution. The resulting mixture was stirred at room temperature overnight. The mixture was then hydrolyzed with water, a few drops of HCl (10%) and extracted with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica gel, pentane), to afford compound **2g** (551.2 mg, 47%) as a colorless liquid and a mixture of **2g**/**3g** (510 mg, 42%). An *ee* value of 95% was measured by chiral SFC with an OJ-H column (program: 2% MeOH-1′-2–15%, 175 bar, 2 mL min^{-1}, 30°C). t_R = 6.25 (*S*) and 6.53 (*R*); $[\alpha]_D^{20}$ = +3.0 (*c* = 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 6.80–7.80 (m, 8H), 6.27 (m, 1H), 5.30 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.06 (dd, *J* = 10.4 Hz, 1H), 4.71 ppm (d, *J* = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 143.5, 142.0, 139.4, 132.3, 130.5, 130.3, 130.2, 128.6 (2C), 128.4 (2C), 128.0, 126.8, 117.3, 54.0 ppm.

(*R*,*E*)-Methyl 4-(3,4-dichlorophenyl)-4-phenylbut-2-enoate (6): Compound **2g** (551.2 mg, 2.1 mmol, 1 equiv) was added, under argon, to a flask containing CH_2Cl_2 (3 mL). Methylacrylate (0.43 mL, 4.75 mmol, 2.3 equiv) and catalyst **5** (29.8 mg, 2.3%) were then added and the mixture was stirred at reflux overnight before being diluted with Et_2O and hydrolyzed with HCl (10%). The organic layer was separated and the aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (silica, pentane/Et_2O 9:1), affording the desired compound **6** as a colorless oil (568.1 mg, 84%). $[\alpha]_D^{20}$ = +1.0 (*c* = 1.12 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.40–7.20 (m, 6H), 7.15 (d, 2H, *J* = 7.8 Hz), 7.01 (d, *J* = 8.1 Hz, 1H), 5.76 (d, 1H, *J* = 15.6 Hz), 4.84 ppm (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 165.2, 148.5, 141.7, 140.2, 133.3, 131.0, 130.5, 130.3, 128.8 (2C), 128.4 (2C), 127.9, 127.3, 123.2, 52.2, 51.6 ppm.

(*R*)-Methyl 4-(3,4-dichlorophenyl)-4-phenylbutanoate (7): $Cu(OAc)_2{\cdot}H_2O$ (3.8 mg, 5%) and (±)-BINAP (12.6 mg, 5%) were added to a flask containing THF (4 mL). After stirring for 5 min, poly(methylhydrosiloxane) (100 μL, 1.62 mmol, 4 equiv) was added into the flask, followed by **6** (130.1 mg, 0.405 mmol, 1 equiv) and *t*BuOH (124.3 mg, 1.62 mmol, 4 equiv). The resulting mixture was stirred at room temperature for 5 h and concentrated in vacuo. The crude mixture was purified by flash column chromatography (silica gel, pentane/Et_2O 9:1) affording compound **7** as a colorless oil (130.9 mg, 100%). $[\alpha]_D^{20}$ = −6.1 (*c* = 1.12 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.36–7.20 (m, 7H), 7.08 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.91 (t, *J* = 7.3 Hz, 1H), 3.65 (s, 3H), 2.35 (m, 2H), 2.27 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 173.4, 144.5, 142.6, 132.4, 130.3, 130.2, 129.6, 128.7, 127.6, 127.1, 126.8, 51.5, 49.5, 32.1, 30.1 ppm.

Typical procedure for allylic arylation of carbonate 9b

*(S)-Cyclohex-2-enylbenzene (**10**)*: (According to Table 8, entry 15) In a flame-dried Schlenk tube, the chiral ligand **L14** (0.02 mmol, 0.04 equiv), [{IrCl(cod)Cl}$_2$] (6.7 mg, 0.01 mmol, 0.02 equiv), and freshly sublimed TBD (5.6 mg, 0.04 mmol, 0.08 equiv) were dissolved in dry THF (0.5 mL). The resulting orange solution was stirred for 2 h at room temperature under a nitrogen atmosphere. Acetate **9b** (70.1 mg, 0.5 mmol, 1 equiv) was added and the mixture was stirred for 15 min. During this time another solution was prepared in a second flame-dried flask containing freshly dried $ZnBr_2$ (112.6 mg, 0.5 mmol, 1 equiv), LiBr (86.8 mg, 1 mmol, 2 equiv), and dry THF (2 mL). The phenyl Grignard reagent (1 mL, 1 mmol, 2 equiv) was added to the latter flask and the resulting solution was stirred for 2 h before being introduced into the first Schlenk flask. The combined mixture was stirred overnight at 40°C and quenched with a saturated aqueous solution of NH_4Cl (10 mL). The product was extracted with Et_2O (3×10 mL) and the organic layer was dried and concentrated in vacuo. The crude product was purified on a silica gel chromatography column (cyclohexane) and **10**[10e] was isolated as a colorless liquid (62 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.36–7.23 (m, 5H), 5.93 (m, 1H), 5.75 (m, 1H), 3.44 (m, 1H), 2.14–1.55 ppm (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 146.7, 130.2, 128.4, 128.3, 127.8, 126.0, 41.9, 32.7, 25.1, 21.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3064, 3009, 2932, 2860, 1601, 1491, 1450, 737, 702 cm^{-1}; MS (EI): *m*/*z* (%): 158 (100) $[M]^+$, 143 (57), 129 (95), 115 (57), 104 (18), 91 (28).

Typical procedure for allylic arylation of dibromide 16

*(S)-(1-Bromobut-3-en-2-yl)benzene (**17**)*: (According to Table 9, entry 8) In a flame-dried Schlenk tube, chiral **L8** (*aR*,*SS*) (21.6 mg, 0.04 mmol, 0.08 equiv), [{IrCl(cod)Cl}$_2$] (13.4 mg, 0.02 mmol, 0.04 equiv), and freshly sublimed TBD (5.6 mg, 0.04 mmol, 0.08 equiv), were dissolved in dry THF (0.5 mL). The resulting orange solution was stirred for 2 h at RT until intense red coloration appeared. Immediately following the coloration, the substrate (106 mg, 0.5 mmol, 1 equiv) was added to the Schlenk tube and the mixture stirred for 15 min. During this time another solution was prepared in a second flame-dried flask containing freshly dried $ZnBr_2$ (112.6 mg, 0.5 mmol, 1 equiv) and LiBr (86.8 mg, 1 mmol, 1 equiv) in dry THF (2 mL). The phenyl Grignard reagent (1 mL, 1 mmol, 2 equiv) was then added to the flask and the resulting mixture was stirred for 2 h before being introduced into the first Schlenk. The combined reaction mixture was stirred at RT for 2 min before Et_2O (10 mL) and a saturated aqueous solution of NH_4Cl (10 mL) were added to the reaction mixture. The organic layer was washed with brine (10 mL) and water (10 mL), then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified on silica gel chromatography column (SiO_2, pentane, R_f = 0.79) to recover products **17** (89 mg). Enantiomeric excesses was measured by chiral GC with a Chirasil-Dex CB, Helium flow instrument (program: 70–0–1–170) t_R = 47.55 (−), 48.33 (+); $[\alpha]_D^{22}$ = −22.18 (*c* = 0.28 in $CHCl_3$) for 65% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.38–7.34 (m, 2H), 7.30–7.29 (m, 1H), 7.28–7.22 (m, 2H), 6.03 (ddd, *J* = 10.4, 7.3, 17.4 Hz, 1H), 5.22 (dd, *J* = 1.0, 10.4 Hz, 1H), 5.17 (dd, 1H, *J* = 1.3, 17.2 Hz), 3.71 (m, 1H), 3.65 (s, 1H), 3.63 ppm (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 141.32, 138.6, 128.9, 128.9, 127.8, 127.8, 127.4, 117.2, 51.9, 36.5 ppm; IR (neat): $\tilde{\nu}$ = 3063, 2959, 2923, 1873, 1640, 1601, 1493, 1453, 1416, 1258, 1220, 1074, 989, 920, 762, 748, 698, 650 cm^{-1}; MS (EI) *m*/*z* (%): 212 (21), 210 (21), 154 (17), 131 (22), 118 (20), 117 (100), 116 (14), 115 (42), 91 (30), 77 (16), 51 (19); HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}Br$: 210.0044; found = 210.0044.

All other products are described in the Supporting Information, including chromatographic and spectral data.

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