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Iridium-Catalyzed Asymmetric Allylic Substitution with Aryl Zinc Reagents

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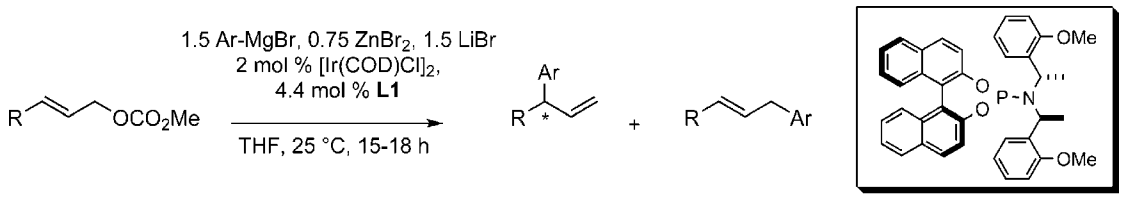
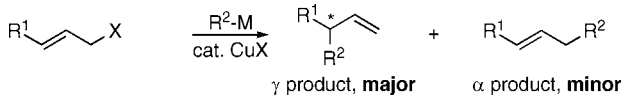
ABSTRACT



Thanks to iridium catalysis, arylzinc reagents undergo regioselective allylic substitution with very high enantioselectivity, when associated with phosphoramidite ligands.

The allylic substitution is a fundamental reaction in organic chemistry.[1] The reaction of carbon nucleophiles is usually catalyzed by a transition metal, and chiral ligands around this metal may allow the asymmetric version of this reaction.[2] Copper is unique in this context, allowing nonstabilized nucleophiles, such as alkyl groups, to be transferred.[3] In addition, the regiocontrol of the reaction, with unsymmetrically substituted allylic substrates, is possible with this metal.[4] We, and others, have developed efficient copper-catalyzed procedures where a Grignard or a dialkylzinc reagent reacts, enantioselectively, with an allylic substrate with high regio- and stereocontrol (Scheme 1).[5]

Scheme 1



The γ product could be obtained with >99:1 regioselectivity and >98% enantioselectivity with many alkyl Grignards or alkylzinc reagents, thanks to a chiral ligand to copper. However, despite all efforts, the transfer of an aryl group was not regioselective, resulting mainly in the achiral α product.

Aryl metal reagents have scarcely been used with other transition metals than copper.[1] There are even fewer enantioselective versions, most of them dealing with meso-type π-allyl systems.[6] For soft nucleophiles, most transition metals show mainly α selectivity on the above type of allylic

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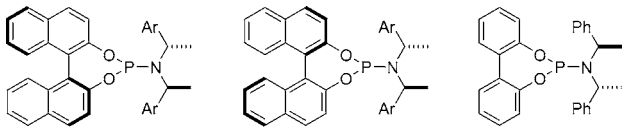
substrates.[1,2] Iridium stands as the most notable exception: γ selectivity, and high enantioselectivity, was found with several heteroatomic nucleophiles as well as with stabilized carbon nucleophiles such as malonates.[7] Remarkably, Evans has found that Rh catalysis allows a moderately regiocontrolled allylation with phenylzinc halide.[8] We report in this Letter that arylzinc reagents can be catalyzed by chiral iridium complexes to afford, for the first time, the γ product as the major regioisomer, along with good to excellent enantiocontrol.

Since arylzinc halides are known to be compatible with palladium catalysis,[6] we felt that their association with a γ selective metal, such as Ir, could provide the desired regioselective substitution. In addition, our phosphoramidite ligand **L1** (Figure 1) affords excellent enantioselectivities with this metal.[9]

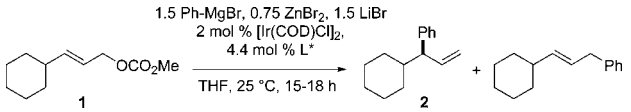


L1 Ar = *o*-MeO-C_6H_4 **L2** Ar = *o*-MeO-C_6H_4 **L5**
L3 Ar = Ph **L4** Ar = Ph

Figure 1. Phosphoramidite ligands used in this study.

Carbonate **1** was selected as a typical allylic substrate for our preliminary studies. The experimental conditions were set identical with those used for the allylic alkylation with malonates, that is THF, room temperature for 15−18 h (overnight), 2% of $[Ir(COD)Cl]_2$, and 4.4% of **L1** (Scheme 2).[7g] It appeared that optimum γ selectivity can be attained

Scheme 2



with organozinc reagents prepared either from PhLi or, better, from the corresponding Grignard reagent. Half an equivalent of $ZnBr_2$ is enough. The resulting diphenylzinc is able to transfer both phenyl groups, thus making the reaction more atom economical.[10] Phenyl Grignard itself reacts directly with the carbonyl group of the carbonate. The addition of LiBr has a strongly beneficial effect, as was the case for malonates.[7b,g] Changing the leaving group (acetate, halide, phosphate) gave lower selectivities.

This first screening identified the best experimental conditions for increased γ selectivity. Further screening was performed on many chiral and achiral phosphorus ligands (Figure 1) to identify how the structural variation of the ligand may affect both the regio- and enantioselectivity. **L1** and **L3** gave the best results (69/31, ee 74% and 47/53, ee 66%) in favor of the γ product. A strong match/mismatched effect was observed with **L2** and **L4** (30/70, ee 84% and 13/87, ee 80%) where the ee increased while the regioselectivity strongly dropped. In both cases the absolute configuration remained the same, meaning that the amine part of the ligand imposes the stereochemistry of the product. Finally, the first ligand we tried, **L1**, appeared to be the best compromise between high γ selectivity and enantioselectivity.

We next turned our attention to the scope of the reaction (Table). First, several substrates were tested with various alkyl or aromatic groups. On the other hand, different aryl groups were introduced via their Grignard reagent, or sometimes via their organolithium reagent. The reaction with phenylzinc reagent seems quite general with aryl-substituted substrates. The enantioselectivities usually reach >90%, with one example at 99.2% (entry 7)! The regioselectivities are

Table 1. Reaction of Arylzinc Reagents with Various Allylic Carbonates, with **L1**

entry	substrate	product	convn (yield, %)	γ/α	ee, %
1	**1**	**2**	100 (72)	69/31	74 (S)
2	**3**	**4**	100	42/58	78 (S)[a]
3	**5**	**6**	100 (67)	49/51	90 (S)[a]
4	**5**	**6**	100	23/77	85 (S)[b]
5	**7**	**8**	100 (78)	33/67	91 (S)[a]
6	**7**	**8**	100	15/85	56 (S)[b]
7	**9**	**10**	100 (83)	55/45	99.2 (S)[a]
8	**11**	**12**	100 (89)	57/43	95 (R)
9	**13**	**14**	100 (83)	50/50	93 (R)
10[c,d]	**15**	**16**	100 (98)	56/44	97 (S)[a]
11	**17**	**18**	100 (93)	53/47	92 (R)
12	**19**	**20**	100	73/27	79 (S)[a]
13	**21**	**18**	100 (97)	63/37	91 (S)
14	**21**	**10**	98	16/84	63 (R)[a]
15	**21**	**14**	100 (95)	45/55	82 (S)
16	**21**	**16**	100 (78)	40/60	80 (S)
17	**11**	**22**	100 (51)	32/68	86 (S)

[a] **Ent-L1** was used. [b] With **Ent-L2**. [c] The same experiment with the Grignard prepared by Mg/I exchange[11] gave 87% isolated yield, with 46/54 selectivity and 78% ee. [d] The same experiment with PhLi prepared by Li/I exchange gave 53% isolated yield, with 44/56 selectivity and 87% ee.

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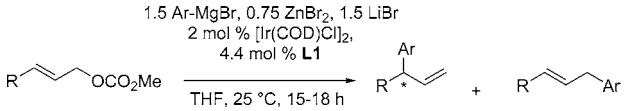
usually slightly above 50%, but it should be noted that such values are unprecedented. An ortho heteroatom on the substrate, such as *o*-MeO-C_6H_4 **3** (entry 2) or 2-furyl **19** (entry 12), lowers the ee values to 78% and 79%, while, for an unexplained reason, a *p*-MeO-C_6H_4 substituent on substrate **7** (entry 5) lowers the regioselectivity. The matched/mismatched effect of **L1** versus **L2** could be seen again with substrates **5** and **7** where both the regio- and enantioselectivities are lower (see entries 3−4 and 5−6). In general, we do not see any marked effect of the electron withdrawing or electron donating nature of the aromatic group (compare entries 5 and 10). In addition, other aryl Grignard reagents were investigated on cinnamyl carbonate **21**. Although commercial grade Grignard reagents were used, it is also possible to use Grignard reagents made according to Knochel, by magnesium−halogen exchange with *i*-PrMgCl·LiCl.[11] As compared to the previous results with Ph_2Zn, the enantioselectivities are slightly lower (63−91%).

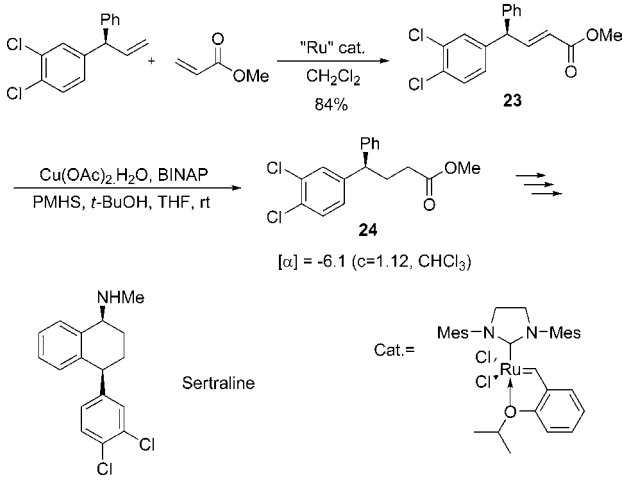
Scheme 3



1	R = cHex		**2**	R = cHex	Ar = Ph
3	*o*-MeO-C_6H_4		**4**	*o*-MeO-C_6H_4	Ph
5	*m*-MeO-C_6H_4		**6**	*m*-MeO-C_6H_4	Ph
7	*p*-MeO-C_6H_4		**8**	*p*-MeO-C_6H_4	Ph
9	*p*-Cl-C_6H_4		**10**	*p*-Cl-C_6H_4	Ph
11	3,4-Cl_2-C_6H_3		**12**	3,4-Cl_2-C_6H_3	Ph
13	*p*-F-C_6H_4		**14**	*p*-F-C_6H_4	Ph
15	*p*-CF_3-C_6H_4		**16**	*p*-CF_3-C_6H_4	Ph
17	2-Naphth		**18**	2-Naphth	Ph
19	2-Furyl		**20**	2-Furyl	Ph
21	Ph		**22**	3,4-Cl_2-C_6H_3	2-Naphth

The absolute configuration of the products of this reaction was determined by comparison with known data on product, **2**.[12,13] In addition, product **14** was submitted to cross-metathesis reaction with methyl acrylate[14] and the Grubbs−Hoveyda catalyst (Scheme 4).[15] The resulting ester **23** was reduced to **24**, a well-known intermediate[16] in the synthesis of Sertraline (Zoloft), a major pharmaceutical agent for the treatment of depression.[17] The reduction of the double bond

Scheme 4 . Synthetic Approach to Sertraline



was done by conjugate addition of a CuH species.[18] A Pd-catalyzed hydrogenation was avoided due to potential racemization of this sensitive substrate.[19]

The stereochemical outcome merits some comments. The selected face attack by the diarylzinc species is exactly the same as the face selectivity of malonates and amines we observed previously.[7h] Does that mean that the mechanism of the substitution is the same? The lower regioselectivity we observe in these reactions may point to a divergent mechanism for the γ and the α products. The γ product could arise from an anti attack of the intermediate π-allyliridium complex, whereas the α product could be the result of a prior transmetallation with the zinc nucleophile.[11] Studies to clarify this point are currently under investigation.

In conclusion, we have disclosed the first Ir-catalyzed regioselective allylic substitution with aryl nucleophiles, with high enantioselectivity. Although moderate, the observed γ regioselectivity is the highest reported to date for such a reaction, whatever the metal. The obtained diaryl-substituted chiral alkenes are useful synthetic intermediates, as exemplified by the formal synthesis of Sertraline.

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Supporting Information Available: Experimental procedures and spectral analyses of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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