Asymmetric Synthesis

A Highly Effective Phosphoramidite Ligand for Asymmetric Allylic Substitution[**]

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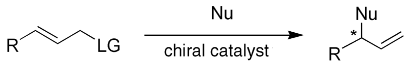
Asymmetric allylic substitution [Eq. (1)] is a potentially powerful method for creating chiral centers in readily available starting materials. Great efforts have been made to control the chemo-, regio-, and enantioselectivities of the reaction products.[1]

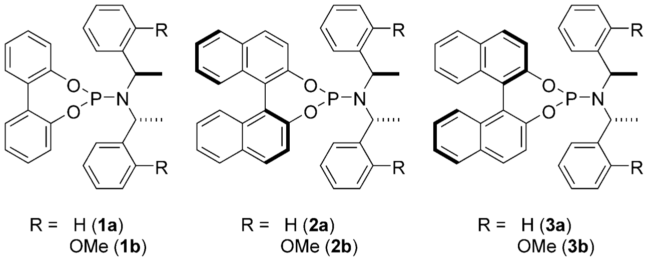


(1)

In contrast to other metals (Pd, Mo, and Ir, for example),[2] copper allows harder nucleophiles, such as alkyl groups, to be used. Increasing interest is being shown in catalytic systems where the copper center is coordinated to a chiral ligand,[3] such as with Grignard[4] and organozinc reagents.[5]

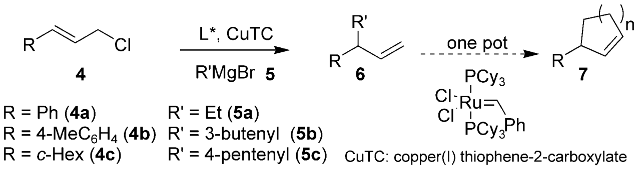
The research in our group has focused on the development of efficient ligands for the substitution of allylic chlorides by Grignard reagents. Previously, we showed that phosphorus ligands derived from tetraaryl-1,3-dioxolane-4,5-dimethanol (taddol) were highly effective chiral reagents in the reaction with cinnamyl chloride ($\gamma/\alpha = 94/6$, 73% *ee*).[4d] Our second-generation phosphoramidite ligands improved on this result, with an *ee* value of 79% being observed. They also allowed a wider scope of applicability.[4e] Herein, we report new phosphoramidite ligands for the same application that are also compatible with our previously described one-pot Ru-catalyzed metathesis procedure.[4e] These third-generation ligands give *ee* values of up to 96% in most cases and can be applied to Ir-catalyzed allylic substitution.

The biphenol **1a**[6] and binaphthol-based ligands **2a** and **3a**[7] (see Scheme 1) were used as the starting compounds, and related ligands were prepared by structural modifications, either at the biphenol (or binaphthol) or the amino functionality. Ligands **1b**–**3b** (Scheme 1) which contain an amine group as well as *ortho*-methoxy substituents on the phenyl rings[8] provided greatly improved results both in the regioselectivity and the enantioselectivity of the products. Previously, [4e] we showed that **1a** gave an *ee* value of 79% and a regioselectivity of 91:9 in favor of the γ product resulting from the addition of **5a** to **4a** (Table 1, entry 1). The binaphthol-based ligand **2a** induced a similar enantioselectivity although the regioselectivity was poorer (entry 2). The reaction with ligand **3a** was not as regioselective, but did not invert the absolute configuration of **6** (entry 3). For this case we could hypothesize that the amine functionality in the ligand dictates the absolute configuration of the product. This is in contrast to the behavior of these ligands in conjugate addition.[6] The modified ligand **1b**, in comparison with **1a**, gave an increased regioselectivity (98/2) and a similar enantioselectivity (entry 4). Two diastereomeric ligands **2b** and **3b** containing binaphthol units were also prepared to evaluate the effect of a fixed atropoisomerism.



Scheme 1. Phosphoramidite ligands.

Table 1: Enantioselective Cu-catalyzed allylic substitution.



Entry	R	R′	L*	Conv. of **4** [%][a]	S_N2'/ S_N2[b]	*ee* of **6** [%][c]	Yield of **7** [%]	*ee* of **7** [%][c]
1[d]	**4a**	**5a**	**1a**	>99	91/9	79(*S*)	–	–
2	**4a**	**5a**	**2a**	>99	72/28	77(*S*)	–	–
3	**4a**	**5a**	**3a**	>99	79/21	55(*S*)	–	–
4	**4a**	**5a**	**1b**	>99	98/2	74(*R*)	–	–
5	**4a**	**5a**	**2b**	>99	73/27	46(*S*)	–	–
6	**4a**	**5a**	**3b**	(86)	99/1	96(*R*)	–	–
7	**4a**	**5b**	**3b**	(83)	96/4	92(*R*)	77	92(*R*) (61)[e]
8	**4a**	**5c**	**3b**	(81)	91/9	96(*R*)	69	96(*R*) (72)[e]
9	**4b**	**5a**	**3b**	(85)	99/1	96(*R*)	–	–
10	**4b**	**5b**	**3b**	(83)	97/3	93(*R*)	79	93(*R*) (64)[e]
11	**4b**	**5c**	**3b**	(86)	91/9	94(*R*)	72	94(*R*) (76)[e]
12	**4c**	**5a**	**3b**	(82)	>99/1	91(–)	–	–

[a] In parentheses: yields after chromatographic isolation on silica gel. [b] Determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures. [c] Determined by chiral supercritical fluid chromatography or gas chromatography. [d] Already published results.[4e] [e] In parentheses: best results obtained previously.[4e]

Although ligand **2b** gave poor regio- and enantioselectivities (entry 5), ligand **3b** gave spectacular results (entry 6), with excellent regioselectivity (99/1) and enantiomeric excess (96%) being demonstrated. This is the highest reported *ee*

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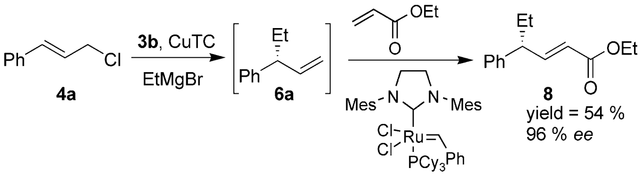
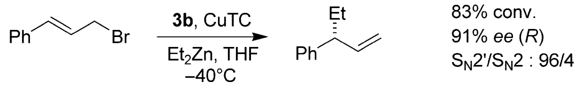
value in this product (formation of **6a** with diethylzinc: 40,[5e] 52,[5b] 66,[5c] and 77 % *ee*[5d]; with Grignard reagents: 42,[4c] 73,[4d] and 82 % *ee*[4e]). Surprisingly, the presence of the methoxy substituent at the *ortho* position of the amine unit in the ligand resulted in an inversion of the absolute configuration of the adduct. It may be tentatively speculated that ligands **1b**–**3b** act as bidentate P,O ligands.[9]

Other Grignard reagents and substrates tested gave equally good results. It should be noted that a correspondingly high enantioselectivity was attained with allylic chloride **4c** containing an alkyl substituent, which is an unprecedented result for such a substrate. Of particular interest is the one-pot, ring-closing metathesis procedure,[4e] with which the Grubbs catalyst is compatible[10] (entries 7, 8, 10, 11). An intermolecular one-pot metathesis of **6a** using three equivalents of ethyl acrylate and 5 mol % of the Grubbs catalyst[10] gave **8** in 96 % *ee* and 54 % yield (Scheme 2). All the results obtained from Grignard reagents of 3-butenyl and 4-pentenyl were greatly improved both in terms of regioselectivity and enantioselectivity (92–96 % *ee* compared to 61–76 % *ee*).



Scheme 2. Intermolecular one-pot metathesis.

The asymmetric Cu-catalyzed allylic substitution may also be performed with dialkylzinc reagents.[5] Ligand **3b** affords excellent results in this reaction (Scheme 3), and outperforms any previous ligand described for diethylzinc and a cinnamyl derivative. The fact that both organometallic reagents afford a similar level of asymmetric induction is unprecedented in copper-catalyzed allylic substitution.

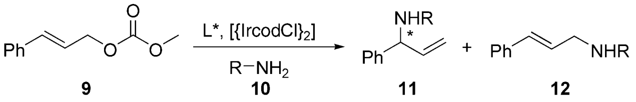


Scheme 3. Asymmetric Cu-catalyzed allylic substitution using diethylzinc.

Many research groups have developed achiral and chiral allylic substitutions catalyzed by iridium.[11] Strong π-accepting monodentate ligands, such as **1a**–**3a**, have been shown to be very efficient.[12] We were curious as to how ligands **1b**–**3b** would perform in the Ir-catalyzed allylic amination of carbonate **9**. Our results are summarized in Table 2.

Relative to ligand **1a** (entry 1), the presence of the methoxy substituent in the amine moiety of the biphenol-based ligand **1b** increased the enantioselectivity without loss of regioselectivity, and a strong acceleration of the reaction was observed. In contrast to the Cu-catalyzed allylic alkylation reaction described above, there was no inversion of configuration in **11**. Clearly, the mechanistic pathways involving copper and iridium are different.

Table 2: Enantioselective Ir-catalyzed allylic amination.



benzylamine (**10a**), allylamine (**10b**), *n*-hexylamine (**10c**)

Entry	Amine	Ligand[d]	Conv. [%][a]	**11**/**12**[b,d]	*ee* [%][c,d]
1	**10a**	**1b** [**1a**]	92(–)	99/1 [98/2]	92(*R*)[87(*R*)]
2	**10a**	**2b** [**2a**]	62(–)	50/50 [94/6]	47(*S*)[75(*S*)]
3	**10a**	**3b** [**3a**]	98(88)	98/2 [99/1]	97(*R*)[95(*R*)]
4	**10b**	**3b** [**3a**]	>99(91)	99/1 [n a]	97(–)[97(–)]
5	**10c**	**3b** [**3a**]	>99(89)	98/2 [98/2]	98(*R*)[96(*R*)]

[a] In parentheses: yields after chromatographic isolation on silica gel. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. [c] Determined by chiral supercritical fluid chromatographic or gas chromatographic analysis of the corresponding acetamide. [d] In square brackets: the results from the study by Ohmura and Hartwig.[12a] cod = cycloocta-1,5-diene.

Ligands **2b** and **3b** with fixed atropoisomerism were also tested to verify which was the best ligand. It is clear from entry 2 that ligand **2b** is the least successful. Ligand **3b** (entry 3) gave an excellent result, even slightly better than **3a**. The same reaction conducted with two other amines confirmed this observation (entries 4 and 5).

The strong acceleration in the reaction rate was again observed, particularly for ligand **3b** (Figure 1). There was not an induction period here, as was the case of **3a** (as described by Hartwig and co-workers).[13] An induction period was observed for the analogue of **3b** with a *para*-methoxy subsitutent, which shows the importance of the position of the methoxy substituent and suggests there is a chelation effect.

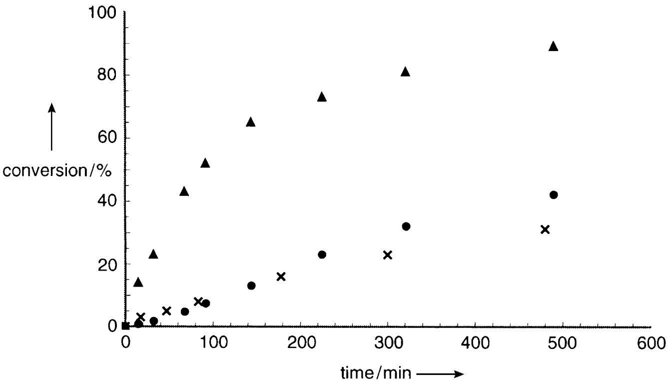


Figure 1. Comparison of the kinetics of the reactions of between ligand **3a** (×), an analogue of **3b** with a *p*-OMe substituent (●), and **3b** (▲) in an iridium-catalyzed asymmetric allylic substitution.

It should be pointed out that the atropoisomerically flexible biphenol-based ligands **1a** and **1b** afforded a product that always has the same absolute configuration as the binaphthol-based ligand **3b**. This is true for the Cu-catalyzed conjugate addition[6] and allylic substitution, as well as for the

Ir-catalyzed allylic substitution, despite the fact that the most efficient ligand belongs to the diastereomerically opposite **2** or **3** series. Therefore, it must be concluded that the biphenol entity changes its conformation to adopt that of ligand **3b**.

In conclusion, we have described a new and highly efficient ligand for two very different applications: first, the copper-catalyzed enantioselective allylic alkylation by Grignard or organozinc reagents on allylic substrates, and second, the iridium-catalyzed enantioselective allylic amination of cinnamyl carbonate. Enantiomeric excesses of up to 96 and 98 % were obtained in the first and second applications, respectively.

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