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Copper catalyzed enantioselective allylic substitution by MeMgX

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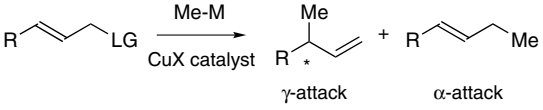
Abstract—Methyl Grignard undergoes highly regio (>90/10) and enantioselective (ee 91–96%) copper catalyzed allylic substitution on cinnamyl-type chlorides. 3% of CuBr and 3.3% of a chiral phosphoramidite ligand are sufficient for a complete reaction. The synthesis of a precursor of (+)-Naproxen is described. The reaction can be extended to alkyl substituted allylic chlorides (ee 72%).

1. Introduction

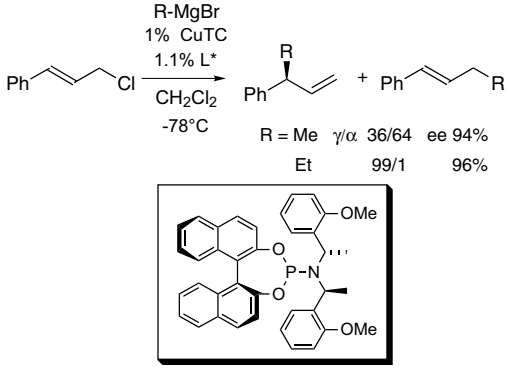
Among the metal-catalyzed allylic substitution reactions,[1] copper plays a prominent role due, not only to the high regio and stereoselectivity it provides, but also because it allows harder nucleophiles, such as Grignard or organozinc reagents, to be used.[2] Thus, simple alkyl groups can only be introduced with copper catalysis. The enantioselective version has found strong interest in the last 4–5 years, both with Grignard[3] or diorganozinc reagents.[3e,4] High regio and enantioselectivities could be attained, with a variety of substrates, leaving groups (LG) or RMgX, and R_2Zn groups.

The only difficult group to introduce is the methyl group, though it is the most valuable, from a synthetic point of view. The difficulty lies either on the poor enantioselectivity,[5] or the low reactivity[6] or the bad regioselectivity.[7] (Scheme 1)



Scheme 1. Copper catalyzed allylic substitution.

We have recently disclosed a new phosphoramidite ligand, which affords the highest reported enantioselectivities (91–96%) for cinnamyl-type substrates, using either Grignard or dialkylzinc reagents and 1% Cu-thiophene carboxylate (and 1.1% L*).[3e] However, in the case of MeMgBr, the regioselectivity was in favor of the undesired achiral α-product, although the enantioselectivity of the γ-product was excellent (Scheme 2).



Scheme 2. Enantioselective copper catalyzed allylic substitution.

We report herein our successful efforts to improve this regioselectivity and render this transformation synthetically useful.

2. Results

The regioselectivity of the copper catalyzed allylic substitution has been extensively studied.[2,8] It highly depends on the copper source, its amount, the solvent, and various additives, such as $BF_3{\cdot}OEt_2$.[9] It is commonly believed that copper reagents favor the S_N2' adduct, whereas cuprate reagents are not selective, the

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Table 1. Influence of the copper salt[a]

Entry	Copper salt	Conv.	γ/α	ee (%)
1	CuTC[b]	100	49/51	95
2	CuCl	93	60/40	95
3	CuBr	100	54/46	95
4	CuI	92	49/51	94
5	CuBr, Me_2S	100	52/48	94
6	CuCN	10	45/55	46

[a] Slow addition (2 h) at −78 °C, in CH_2Cl_2.
[b] CuTC stands for copper thiophene carboxylate.

Table 2. Influence of the rate of addition[a]

Entry	Copper salt	Add. time	Conv.	γ/α	ee (%)
1	CuTC[b]	40 min	100	36/64	94
2	CuBr	40 min	100	38/62	94
3	CuTC[b]	2 h	100	49/51	95
4	CuBr	2 h	100	54/46	95
5	CuTC[b]	4 h	100	81/19	95
6	CuBr	4 h	100	**83/17**	**96**

[a] Addition at −78 °C, in CH_2Cl_2.
[b] CuTC stands for copper thiophene carboxylate.

formed product is at the least substituted carbon (in our case, the adduct). Therefore, in a catalytic reaction the rate of addition of the Grignard reagent is very important. A fast addition allows the formation of a cuprate intermediate. In contrast, a slow addition would prevent the formation of a cuprate species by letting the organocopper intermediate react with the allylic substrate.[8c] These parameters were investigated with cinnamyl chloride as typical substrate and the ligand shown in Scheme 2. Table 1 summarizes our results with various copper sources, under the standard conditions, and Table 2 shows the results of different addition rates of MeMgBr.

Although it is known that CuCN favors the S_N2' process,[2c,8,10] it was surprising to see that the regioselectivity was not improved (Table 1, entry 6). Instead, both the conversion and the enantioselectivity were much lower than with the other copper salts. It was also interesting to observe that all the other copper salts gave roughly similar results, with always good enantioselectivity. For this reason we selected CuBr as another copper source (much cheaper), along with CuTC, which was our favorite until now.[3d,e]

The influence of the addition rate of the Grignard reagent was more instructive (Table 2). Indeed, as expected, the slower the addition the better was the regioselectivity. An addition over 2 h already brings some improvement (compare entries 3/4 and 1/2), and a syringe pump addition over 4 h gave an acceptable γ/α ratio of 83/17, with an excellent enantioselectivity of 96%.

A last parameter to look at was the amount of catalyst. Table 3 shows the results obtained under the experimental conditions stated in entry 6 (Table 2).

The amount of catalyst plays an important role, as it accelerates the reaction, thus preventing the formation

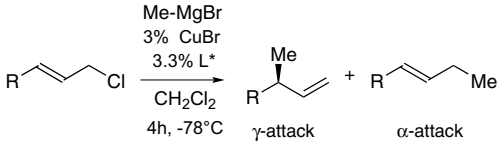
Table 3. Influence of the amount of CuBr catalyst

Entry	% of Catalyst	Conv.	γ/α	ee (%)
1	1	100	83/17	96
2	2	100	87/13	96
3	**3**	100	**89/11**	**96**
4	4	100	89/11	96
5	5	100	89/11	95

of the undesirable cuprate intermediate. The optimum value was found to be 3% of CuBr (and 3.3% of chiral ligand).

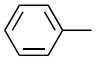
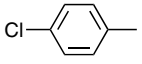
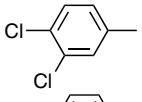
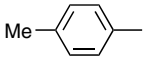
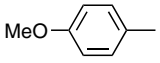
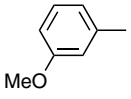
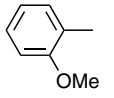
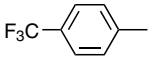
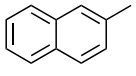
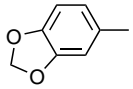
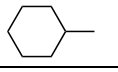
With the optimized conditions in hand, we screened several substrates to generalize the scope of the reaction (Scheme 3 and Table 4).

The enantioselectivity of the reaction is always excellent (ee's > 90%), whatever the electron demand of the sub-



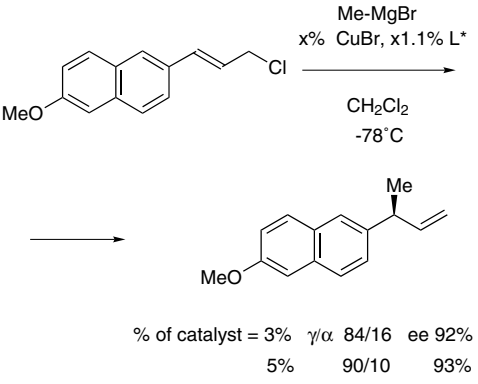
Scheme 3. Enantioselective copper catalyzed allylic substitution (Table 4).

Table 4. Enantioselective substitution on various allylic chlorides

Entry	R	Conv.	γ/α	ee (%)
1		100	89/11	96
2		90	90/10	95
3		94	90/10	94
4		100	90/10	95
5		100	91/9	91
6		100	83/17	90
7		100	84/16	66
8		100	67/33	92
9		100	84/16	93
10		100	90/10	91
11		90	96/4	72

stituent on the aromatic group. Both electron withdrawing (entries 2 and 3) or electron-donating group (entries 4 and 5) are tolerated. Only the *ortho*-methoxy group (entry 7) seems to interfere, perhaps via a coordination to the metal, and the ee drops to 66%. The regioselectivity, although not as high as with normal alkyl Grignard,[3e] is still at acceptable levels with γ-selectivities ranging from 83% to 91%. The reaction has also been extended to a nonaromatic group, with a cyclohexyl substituent (entry 11). The regioselectivity is remarkably high, although the enantioselectivity is lower than with the other aromatic substrates.

An interesting simple application was to apply this method to a formal synthesis of (+)-Naproxen, a well-known nonsteroidal anti-inflammatory drug (Scheme 4).[11] The direct precursor to Naproxen could be obtained under the established standard conditions. However, we were not satisfied with the regioselectivity for such a valuable compound. A simple increase of the catalyst, from 3% to 5%, allowed the desired improvement, with a 90% γ-selectivity and 93% ee.



Scheme 4. Synthesis of the precursor of Naproxen.

3. Conclusion

In summary, we have disclosed an efficient catalytic system for the asymmetric transfer of the methyl group, the most synthetically valuable.[12] The amount of the metal catalyst and the chiral ligand are still at low enough values for copper catalysis.

Acknowledgements

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11. For a review on Naproxen and congeners see: Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *15*, 4095–4131.
12. Typical procedure (for 1 mmol): A dried Schlenk tube was charged with copper salt (3 mol%) and the chiral ligand (3.3 mol%). Dichloromethane (3 mL) was added and the mixture was stirred at room temperature for 30 min. The allylic chloride (1 mmol) was introduced dropwise and the reaction mixture was stirred at room temperature for a further 5 min before being cooled to −78 °C in an ethanol-dry ice cold bath. MeMgBr (3 M in diethyl ether, 1.2 equiv), diluted in dichloromethane (0.6 mL) was added over 4 h via a syringe pump. Once the addition was complete the reaction mixture was left at −78 °C for a further 12 h, at which point gas chromatography of an aliquot showed that all the starting material had been converted. The reaction mixture was quenched by addition of aqueous hydrochloric acid (1 N, 2 mL). Diethyl ether (10 mL) was added and the aqueous phase was separated

and extracted further with diethyl ether (3×3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The oily residue was purified by flash column chromatography (eluent = pentane) to yield the product as a mixture of S_N2' and S_N2 regioisomers. Gas chromatography or supercritical fluid chromatography on a chiral stationary phase showed the enantiomeric excess of S_N2' product. (+)-3(*S*)-(2-(6-Methoxy)-naphthyl)-1-butene: ^{1}H NMR (400 MHz, $CDCl_3$): 7.74–7.17 (m, 6H, Ar*H*), 6.13 (m, 1H, CH_2=C*H*), 5.12 (m, 2H, CH_2=CH), 3.96 (s, 3H, OCH_3), 3.65 (quint, J = 6.82 Hz, 1H, C*H*Ph), 1.49 (d, J = 7.08 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 157.3, 143.4, 140.7, 133.2, 129.2, 129.1, 126.9, 126.8, 125.1, 118.7, 113.3, 105.6, 55.3, 43.1, 20.7. $[\alpha]_D^{20}$ +15.7 (*c* 1.4, $CHCl_3$) for 93% ee. Ee was measured by chiral SFC with a Chiralcel OB-H column (5% MeOH, flow rate 2 mL/min) t_R: 5.91 (*S*), 6.48 (*R*).