Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6135-6138, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01214-8

Arenethiolatocopper(I) Complexes as Homogeneous Catalysts for Michael Addition Reactions

Mayra van Klaveren, François Lambert, Desiree J. F. M. Eijkelkamp, David M. Grove and Gerard van Koten*

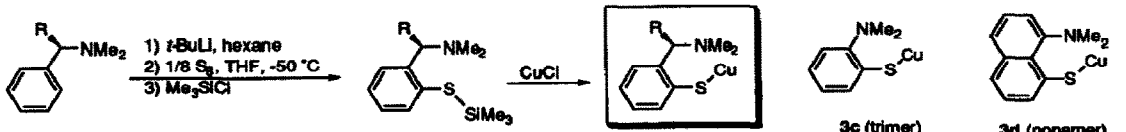
Debye Institute, Department of Metal-Mediated Synthesis, Utrecht University,
Padualaan 8, 3584 CH Utrecht, The Netherlands

Abstract: Arenethiolatocopper(I) complexes are shown to be efficient homogeneous catalysts in Michael addition reactions of several Grignard reagents to acyclic enones; the addition products are formed with excellent chemoselectivity (>99%) and good enantioselectivity (76% e.e.).

An important aspect in contemporary organic chemistry is chemoselective C-C bond formation with high enantioselectivity. This goal has been achieved in Michael addition and cross-coupling reactions that are under substrate control (*e.g.* in prostaglandin synthesis) through the use of an organometallic reagent (RMgX or RLi) combined with stoichiometric amounts of various copper(I) salts (*e.g.* CuCl and CuCN).[1] Only a few examples have been reported in which these reactions are successful when catalytic amounts of a copper(I) salt are used.[2]

We are now developing new types of arenethiolatocopper(I) catalysts (CuSAr, **3a-d**, Scheme 1) for 1,4-addition reactions with enones[3] and 1,6-addition reactions with enyn esters.[4] In these reactions the *ortho*-amino arenethiolate anion has excellent properties as a non-transferable group for obtaining high chemo- and regioselectivity. Recently, in collaboration with Bäckvall *et al.*, we have demonstrated that the use of the arenethiolatocopper(I) catalysts **3** can also afford high chemo- and regioselectivity in cross-coupling reactions.[5]

Scheme 1



1a: R = H
1b: R = Me, e.e. > 99.8%

2a: R = H
2b: R = Me, e.e. > 99.8%

3a: R = H (trimer)
3b: R = Me (trimer), e.e. > 99.8%

We now show the broad applicability of catalysts **3a-d** in Michael addition reactions of Grignard reagents to acyclic enones. Our understanding of this catalytic system has been increased by varying not only the experimental parameters (Section I), but also the steric and electronic properties of the enone (Section II).

I) Studies of the experimental parameters.

Arenethiolatocopper(I) complexes **3** have been employed as catalysts for the 1,4-addition reaction of a Grignard reagent (RMgI) to 4-phenyl-3-buten-2-one **4** (that affords 4-phenyl-3-pentan-2-one **5** after hydrolysis) and this system was used to investigate the influence of (**i**) the addition method, (**ii**) the amount of chiral CuSAr **3b**, (**iii**) the solvent and the presence of additives, (**iv**) the Grignard reagent and (**v**) the exact type of catalyst

(**3a-d**). The results are collected in Table I. Chiral complex **3b** (*R*,*R*,*R*) was prepared as described previously (Scheme 1),[3b] starting from **1b** with an e.e. of >99.8%. The same synthetic strategy (Scheme 1) was used to prepare **3a** (trimer), **3c** (trimer) and **3d** (nonamer).[3c]

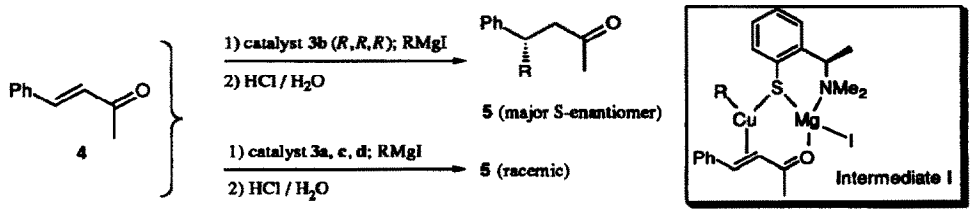


Table I. Influence of experimental parameters in the 1,4-addition of RMgI to **4** using CuSAr catalysts in Et_2O at 0 °C.[a]

Entry	R	Catalyst[b] (mol %)	Conditions [Addition mode[c], Additive[d]]	**5**: Yield[e,f] (%)	(Selectivity)[g] (%)	E.e.[h] (%)
1.	Me	**3b** (9)	[A, none]	41	(43)	45
2.	"	**3b** (9)	[B, none]	78	(78)	0
3.	"	**3b** (9)	[C, none]	97	(97)	76
4.	"	**3b** (4)	[C, none]	83	(83)	70
5.	"	**3b** (9)	[C, none][a]	86	(86)	0
6.	"	**3b** (9)	[C, $SiMe_3Cl$]	65	(65)	70
7.	"	**3b** (9)	[C, $SiMe_3Cl$ + HMPA]	88	(14)	14
8.	"	**3b** (9)	[C, $BF_3{\cdot}OEt_2$]	16	(29)	0
9.	*n*-Bu	**3b** (9)	[C, none]	>95	(>95)	45[i]
10.	*i*-Pr	**3b** (9)	[C, none]	>95	(>95)	10
11	Me	**3a** (9)	[C, none]	95	(95)	-
12.	"	**3c** (9)	[C, none]	93	(93)	-
13.	"	**3d** (9)	[C, none]	93	(93)	-

a) Except for entry 5 which was carried out in THF. b) Amount based on monomeric CuSAr units; (*R*,*R*,*R*) enantiomer of trimeric **3b**. c) See text. d) Added to **4** before use (1 equiv.). e) Conversion is quantative except for entries 1 (95 %), 8 (56 %) and 10 (98 %).Yield determined by capillary GC with phenylacetone as internal standard. f) The only other side products are a result of enolate formation.[6] g) Selectivity = Yield / Conversion. h) E.e. of **5** ((*S*)-enantiomer) determined by capillary GC with a chiral column. i) Determined by ^{13}C NMR of the corresponding ketal with (*R*,*R*)-(-)-2,3-butanediol.

(**i**) Addition method: To obtain the best possible chemo- and enantioselectivity, three addition methods have been investigated (A, B and C) for our system using MeMgI as reagent and 9 mol% of chiral CuSAr **3b** (based on monomeric copper units). Addition method A, involving the addition of MeMgI to an ethereal solution of **4** and **3b** (entry 1) results in a 41% yield of **5** with an e.e. of 45% ((*S*)-enantiomer). In addition method B, where **4** is added to an ethereal solution of MeMgI with **3b**, a 78% yield of **5** with an e.e. of 0% is obtained (entry 2). The best addition method is method C, which involves the controlled, simultaneous addition of solutions of MeMgI and of **4** (at equal concentration) to catalyst **3b** in Et_2O (entry 3). This results in 100% conversion of **4** with a 97% yield of **5** that has an e.e. of 76%. Variation of the other experimental parameters (**ii-v**) in this section (**I**) all employ addition method C.

(**ii**) Amount of chiral CuSAr **3b**: The amount of **3b** in the reaction of **4** with MeMgI significantly influences the chemo- and enantioselectivity: with 9 mol% of **3b** the 1,4-product **5** is obtained in 97% yield with 76% e.e. (entry 3), but with 4 mol% of **3b** it is obtained in only 83% yield with an e.e. of 70% (entry 4).

(iii) Solvent and additives: The chemo- and enantioselectivity of the reaction of MeMgI with **4**, using 9 mol% of **3b**, is dependent on both the solvent and the presence of various additives. With a strongly polar solvent (*e.g.* THF) the e.e. of product **5** is 0% (*cf.* entries 3 and 5). Using additives in the same reaction in Et_2O, *e.g.* $SiMe_3Cl$ (entry 6), $SiMe_3Cl$ with HMPA (entry 7) or the strong Lewis acid $BF_3{\cdot}OEt_2$ (entry 8), results in a lower chemo- and enantioselectivity. These results contrast with literature reports,[2b,7] in which polar additives increase both the chemoselectivity and enantioselectivity of organocuprate reactions.

(iv) Grignard reagent: The scope of these Michael addition reactions has been extended to other Grignard reagents (*n*-BuMgI and *i*-PrMgI) using the optimal parameters found for MeMgI (method C, Et_2O, 0 °C, 9 mol% **3b**). Using *n*-BuMgI and **4**, the corresponding product **5** is formed with more than 95% selectivity with an e.e. of 45% (entry 9). By using *i*-PrMgI in the same reaction **5** is obtained with an e.e. of 10% (entry 10).

(v) Copper(I) catalyst: The non-transferable amino arenethiolate anions in complexes **3a-d** differ with respect to the donor abilities of their N,S-binding sites as well as in the flexibility of the hydrocarbon chain connecting the N- and S-donor atoms. However, despite these differences, these catalysts **3** (entries 11 (**3a**), 3 (**3b**), 12 (**3c**) and 13 (**3d**)) afford a high chemoselectivity in the Michael addition reaction of MeMgI to **4**.

Our results described above for the high chemo- and enantioselectivity of these 1,4-addition reactions with CuSAr catalysts **3** can be explained by the formation of key intermediate **I**[3c,d] (the "active" site in what may be a larger aggregate). In intermediate **I** the enone anchors to the Cu-Mg arenethiolate unit in a bidentate fashion with the double bond coordinating to copper[8] and oxygen coordinating to Mg. In this way the R of RMgX is directed selectively to the 4-position of the enone. The formation of **I** can also be seen as a formal addition of the Mg-C bond over the Cu-S(arene) bond. The results with additives (entries 6, 7 and 8) suggest that **I** can exist in the presence of magnesium enolates but that additives, *e.g.* HMPA, can disrupt the Cu-S-Mg motif. Current studies to further directly elucidate the nature of **I** include solution EXAFS measurements.

II) Studies of the electronic and steric properties of the enone.

Extra insights into the bonding scheme of **I** have been obtained by studying the reaction of MeMgI with various enones that have (i) different para substituents X on the aromatic ring and (ii) different substituents R^1 on the carbonyl group. The results, using the optimal experimental parameters found for the reaction of **4** with MeMgI (method C, Et_2O, 0 °C, 9 mol% of **3b**), are collected in Table II.

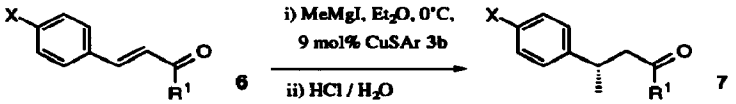


Table II. Variation of X and R^1 of the enone **6** in the 1,4-addition reaction with MeMgI using 9 mol% of **3b**.

Entry	X	R^1	Yield[a,b] of 7 (%)	E.e.[c] of 7 (%)
1.	CN	Me	20	13
2.	Cl	Me	> 99	69
3.	H	Me	97	76
4.	Me	Me	> 99	64
5.	OMe	Me	> 99	56[d]
6.	H	*i*-Pr	98	72
7.	H	*t*-Bu	> 99	45
8.	H	Ph	> 99	0[e]

a) Conversion of **6** is quantitative. Yield determined by capillary GC. b) The side products are a result of enolate formation.[6] c) E.e. of (*S*)-enantiomer determined by capillary GC with a chiral column. d) Determined by ^{13}C NMR of the corresponding ketal with (*R*,*R*)-(-)-2,3-butanediol. e) Determined by optical rotation.

(i) Variation of para substituent X: With either an electron-withdrawing substituent, *i.e.* X = Cl (entry 2), or an electron-donating substituent (X = Me (entry 4) and OMe (entry 5)) the chemoselectivities remain more than 99% to the 1,4-addition products and the e.e.'s of 69% (entry 2), 64% (entry 4) and 56% (entry 5) point to a small effect of the para-substituent X. An exception is X = CN (entry 1) in which both the chemo- and enantioselectivity are very low. These data indicate that the anchoring of the double bond to copper[8] is probably more important for the enantioselectivity than for the chemoselectivity of these Michael addition reactions.

(ii) Variation of R^1 on the carbonyl group: Entries 3, 6, and 7 (R^1 = H, *i*-Pr, *t*-Bu, respectively) show that chemoselectivity is not affected by steric bulk at this position, though the larger R^1 groups do lead to noticeably lower enantioselectivity. In contrast the use of R^1 = Ph (entry 8), which also results in a high chemoselectivity, gives the corresponding 1,4 product with an e.e. of 0%. From this one can conclude that the electronic effects of the R^1 group on the bonding of the enone's alkene and C=O functionalities to the Cu-S-Mg motif in I are probably more important than the steric effects.

The results of this report show the excellent applicability of arenethiolatocopper(I) catalysts **3** in Michael addition reactions. Current research is directed not only to expanding the scope of our catalytic system by employing other chiral arenethiolatocopper(I) catalysts and other substrates such as cyclic enones,[9] but also to determining kinetic effects on the reaction course and enantioselectivity by means of competition experiments.

Acknowledgement: This work was supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

References and Notes:

1. a) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.*, **1987**, *109*, 2040. b) Corey, E. J.; Naef, R.; Hanson, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. c) Rossiter, B. E.; Eguchi, M. *Tetr. Lett.* **1990**, *31*, 965. d) Bertz, S. H.; Dabbagh, G.; Sundararajan, G. *J. Org. Chem.* **1986**, *51*, 4953. e) Alexakis, A.; Mutti, S.; Normant, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 6332.
2. a) Lippard, S. *Organometallics* **1991**, 3178. b) Ahn, K. H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178. b) Tanaka, K.; Matsui, J.; Suzuki, H.; Watanabe, A. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1193.
3. a) Lambert, F.; Knotter, D. M.; Janssen, M. D.; van Klaveren, M.; Boersma, J.; van Koten, G. *Tetr. Asymmetry* **1991**, 2, 1097. b) Knotter, D. M.; Grove, D. M.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1992**, *114*, 3400. c) van Klaveren, M.; Grove, D. M.; van Koten, G. *to be published.* d) van Koten, G. *Pure and Appl. Chem.* **1994**, *in press.* e) Janssen, M. D.; Donkervoort, J. G.; Spek, A. L.; Grove, D. M., van Koten, G. *to be published.* f) van Koten, G. Proceedings of the third symposium in Wurzburg (Vieweg) **1991**.
4. Haubrich, A.; van Klaveren, M.; van Koten, G.; Handke, G.; Krause, N. *J. Org. Chem.* **1993**, *58*, 5849.
5. van Klaveren, M.; Persson, E. S. M.; Grove, D. M.; Bäckvall, J. E.; van Koten, G. *Tetr. Lett.* **1994**, *in press.*
6. Characterization of the dimeric and trimeric enolate side products includes X-ray structure determination: van Klaveren, M.; Lambert, F.; Grove, D. M.; van Koten, G. *to be published.*
7. a) Corey, E. J.; Boaz, N. W. *Tetr. Lett.* **1985**, *26*, 6015 and 6019. b) Alexakis, A.; Berla, J.; Besace, Y. *Tetr Lett.* **1986**, *27*, 1047. c) Johnson, C. R.; Marren, T. J. *Tetr. Lett.* **1987**, *28*, 27. d) Matsuzawa, S.; Horiguschi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. e) Nakamura, E. *Synlett* **1991**, 539.
8. Ullenius, C.; Christenson, B. *Pure and Appl. Chem.* **1988**, *60*, 57.
9. Zhou, Q.; Pfaltz, A. *Tetr. Lett.* **1993**, *34*, 7725.

(*Received in UK* 15 *April* 1994; *revised* 17 *June* 1994; *accepted* 24 *June* 1994)