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Dramatic Improvement of the Enantiomeric Excess in the Asymmetric Conjugate Addition Reaction Using New Experimental Conditions

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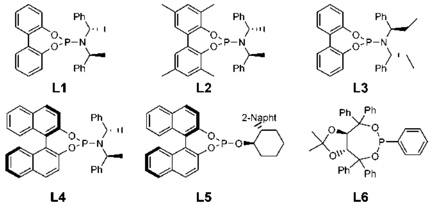
The formation of chiral carbon−carbon bonds by using the asymmetric conjugate addition reaction has been widely investigated.[1] Conditions have been developed, using a catalytic quantity of copper(II) triflate and chiral ligands associated to an organozinc reagent,[2] to perform this reaction in high yield and good to excellent enantioselectivity.[3] Our current objective is to generalize the experimental conditions for a variety of different Michael acceptors.[4]

The optimization of the asymmetric conjugate addition reaction has been realized essentially by examining two parameters: the solvent and the nature of the copper salt, which appear to be crucial to obtain good enantiomeric excess. For example, Sewald reported the use of different copper(I) salts using chiral sulfonamides as ligands and found divergent enantioselectivities according to the Cu source.[5] Using [$Cu(CH_3CN)_4BF_4$], Woodward[6] obtained his best results on *trans*-nonenone with THF as solvent instead of toluene. In the course of our studies on the asymmetric 1−4 addition with new ligands, based on the *induced atropoisomerism* of a simple biphenol unit,[7] we found that new experimental conditions greatly improve the enantiomeric excesses. Moreover, these new conditions also improve many results with known ligands.



(1)

The new ligands L1, L2, and L3 (eq 1) were designed upon hypothesizing that the induced atropoisomerism of the flexible biphenol unit will adopt the configuration of the matched binaphthol-related ligand L4. These ligands were in many cases as good or even better than the parent ligand L4.[7] However, we felt that there was still room for improvement. Thus, we have tested the basic ligand L1 (Scheme 1), the least efficient one, with different copper sources, and in various solvents (Table 1).

Scheme 1

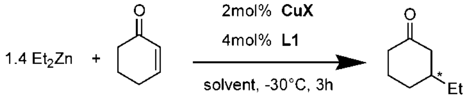
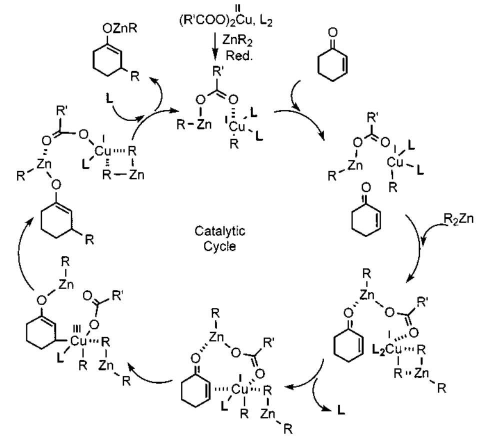


Table 1. Asymmetric Conjugate Addition with L1 on Cyclohexenone with Selected Copper Salts[8]

entry	copper salts	Tol.[a]	Et_2O[a]	CH_2Cl_2[a]	THF[a]	EtOAc[a]
1	$Cu(OTf)_2$	>99%, **82%**	>99%, **90%**	>99%, **72%**	87%, **90%**	92%, **90%**
2	$Cu(acac)_2$	>99%, **80%**	>99%, **90%**	>99%, **82%**	22%, **60%**	82%, **85%**
3	$Cu(OCOCF_3)_2$	>99%, **91%**	>99%, **92%**	92%, **84%**	**80%, 95%**	93%, **90%**
4	$Cu(OAc)_2$	95%, **89%**	>99%, **92%**	94%, **84%**	60%, **90%**	60%, **90%**
5	$Cu(OAc)_2{\cdot}H_2O$	92%, **91%**	>99%,**93%**	90%, **84%**	70%, **90%**	27%, **88%**
6	$Cu(O_2CR)_2$[b]	>99%, **91%**	>99%,**94%**	>99%, **90%**	40%, **80%**	>99%, **93%**
7	CuTC[c]	90%, **93%**	>99%,**96%**	>99%, **90%**	83%, **90%**	>99%, **94%**
8	$Cu(ClO_4)_2{\cdot}6H_2O$	65%, **73%**	>99%, **86%**	>99%, **58%**	98%, **90%**	81%, **85%**
9	$Cu(BF_4)_2{\cdot}6H_2O$	72%, **80%**	70%, **76%**	92%, **60%**	84%, **90%**	63%, **85%**
10	$CuSO_4{\cdot}5H_2O$	23%, **43%**	19%, **43%**	35%, **20%**		
11	CuCl	>99%, **80%**	>99%, **82%**	>99%, **76%**		
12	CuCN	50%, **0%**	>99%, **79%**			
13	CuSPh	>99%, **10%**	97%, **65%**			

[a] Conversion, **ee**. [b] $Cu(naphthenate)_2$. [c] CuTC: copper(I) thiophene-2-carboxylate.

Scheme 2



Both copper(I) and copper(II) species were tested. Copper(II) salts usually have the advantage of being cheaper and easier to handle. The reduction to the true catalytic species Cu(I) is done in situ by Et_2Zn (Scheme 2). All the experiments in Table 1[8] were run under the same experimental conditions, whatever the copper source or the solvent (Cu/ligand ratio 1/2, temperature −30 °C, reaction time 3 h), then quenched with dilute HCl. Some general trends may be readily drawn. First, acetonitrile is not an adequate solvent for the conjugate addition, most conversions being very low.[2a] Second, with the exception of CuCl, CuSPh, and $Cu(ClO_4){\cdot}6H_2O$, most mineral salts gave low conversion and/or low to moderate ee values. All comparisons are made with the previous standard conditions (toluene, $Cu(OTf)_2$), which gave complete conversion and 82% ee (Entry 1).

The solvent study shows that several solvents may be used in this reaction. THF and EtOAc afford high levels of enantioselectivity. However, with both these solvents, the rate of the reaction is slower, although longer reaction time brings the reaction to completion.[2b] Entry 1, with $Cu(OTf)_2$, clearly demonstrates that as far the enantioselectivity is concerned, higher ee values are obtained in ethereal solvents (Ether, THF, and EtOAc). This result contrasts to the usual belief that a noncoordinating solvent, such as toluene, is the most appropriate for the Cu-catalyzed conjugate addition of dialkyl zincs.[2]

In view of previous studies, it was believed that $Cu(OTf)_2$ was the most efficient Cu salt for this reaction.[2,3c,e] This effect has been ascribed to the higher Lewis acidity of this salt as compared to

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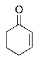
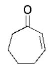
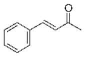
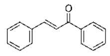
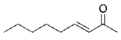
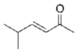
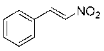
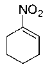
Table 2. Asymmetric Conjugate Addition with L1 to L4

Entry	substrates	Cu salt	L1	L2	L3	L4
1		Cu(OTf)$_2$[a]	82 R	89 R	92 S	98[3a], 95[7] R
		Cu(OAc)$_2$, H_2O[b]	93 R	97 R	97 S	96 R
		CuTC[b]	96 R[c]	**99.0 R**	**99.1 S**	98.7 R
		CuNapht.[b]	94 R	97.8 R	97.4 S	97.7 R
2		Cu(OTf)$_2$[a]	77 R	87 R	91 S	**98 R**
		Cu(OAc)$_2$, H_2O[b]	90 R	93 R	91 S	97 R
		CuTC[b]	95 R	91 R	94 S	96 R
		CuNapht.[b]	92 R	92 R	92 S	96 R
3		Cu(OTf)$_2$[a]	64 S	53 S	34 R	80 S
		Cu(OAc)$_2$, H_2O[b]	80 S	92 S	72 R	**93 S**
		CuTC[b]	80 S	91 S	70 R	90 S
		CuNapht.[b]	82 S	**93 S**	85 R	92 S
4		Cu(OTf)$_2$[a]	27 S	48 S	44 R	**71 S**
		Cu(OAc)$_2$, H_2O[b]	8 S	29 S	29 R	37 S
		CuTC[b]	7 S	10 S	39 R	66 S
		CuNapht.[b]	17 S	**14 S**	32 R	27 S
5		Cu(OTf)$_2$[a]	70 S	77 S	67 R	66 S
		Cu(OAc)$_2$, H_2O[b]	**81 S**	40 S	32 R	59 S
		CuTC[b]	80 S	36 S	48R	26 S
		CuNapht.[b]	45 S	33 S	30 R	14 S
6		Cu(OTf)$_2$[a]	17 R	6 R	17 S	31 R
		Cu(OAc)$_2$, H_2O[b]	65 R	60 R	65 S	77 R
		CuTC[b]	65 R	58 R	60 S	70 R
		CuNapht.[b]	68 R	62 R	70 S	**80 R**
7		Cu(OTf)$_2$[a]	8 R	66 R	34 S	48 R
		Cu(OAc)$_2$, H_2O[b]	66 R	**82 R**	68 S	27 R
		CuTC[b]	62 R	72 R	50 S	10 R
		CuNapht.[b]	60 R	81 R	70 S	10 R
8		Cu(OTf)$_2$[a]	75 (+)	65 (+)	70 (-)	67 (+)
		Cu(OAc)$_2$, H_2O[b]	90 (+)	90 (+)	92 (-)	93 (+)
		CuTC[b]	87(+)	93 (+)	92 (-)	90 (+)
		CuNapht.[b]	92 (+)	**95 (+)**	92 (-)	**95 (+)**

[a] Reaction in toluene. [b] New reactions in ether. [c] 98% ee with Bu_2Zn.

most other Cu salts. We found that Cu carboxylates, either Cu(I) or Cu(II), are even more efficient (entries 2−7). It is clear that the Lewis acid effect is not involved in the degree of enantioselectivity, nor on the reaction rate. A more careful look on the various Cu carboxylates shows that the best Cu salts are Cu$(OCOCF_3)_2$, in THF (Entry 3), Cu$(OAc)_2\cdot H_2O$[9] in ether (Entry 5), and copper thiophene-2-carboxylate (CuTC)[10] in either toluene, ether, or ethyl acetate (Entry 7). The degree of lipophilicity of the Cu salt seems to play some role: copper thiophene-2-carboxylate (CuTC) and Cu naphthenate perform better than Cu$(OAc)_2$. Cu naphthenate is a particularly interesting salt, as it is soluble even in hydrocarbon solvents. It is also interesting to note that Cu$(OAc)_2\cdot H_2O$ is slightly better than Cu$(OAc)_2$. Whether the water molecule plays any role is still an open question.[11] Finally, a comparison of the cost of the Cu salt is worth noting: Cu$(OAc)_2\cdot H_2O$ and Cu naphthenate, the cheapest salts, are also among the best.

We believe that, by analogy to copper sulfonamide,[12] Cu-carboxylates serve as efficient bridge for a mixed zinc cuprate complex, the active nucleophilic species (Scheme 2).

Having established the most appropriate experimental conditions for cyclohexenone, we examined the behavior of other Michael acceptors. The experiments were performed with Cu$(OAc)_2\cdot H_2O$, Cu naphthenate (the cheapest), and copper thiophene-2-carboxylate (CuTC) (the most efficient), in Et_2O solvent, and with all three ligands L1, L2, and L3. In addition, the parent ligand L4 was also tested under the same conditions. All reactions were carried out until complete conversion, and the results are shown in Table 2.

Cyclohexenone is usually the standard substrate for testing the asymmetric conjugate addition. Ligands L2 and L3 gave greatly improved results with the highest reported ee of 99.1%, thus surpassing the parent ligand L4 (Entry 1). Although cycloheptenone followed the same trend, the best ee was 95%, with L1 (Entry 2). With the exception of chalcone (Entry 4), acyclic enones gave spectacular improvements of the enantioselectivity. Thus, benzalacetone (Entry 3) gave 93% ee with L2 (from 53% under the previous conditions) and 93% with L4 (from 80% ee). *trans*-Nonenone (Entry 5) gave 81% ee with L1. It should be pointed out that ligand L5 also gave an improved result with 70% ee, from 57% on the *trans*-nonenone with CuTC.[4a] The ee of 5-methyl-3-hexen-2-one (Entry 6) went up to 80% (L4), instead of 31% under the previous conditions.[4a]

Similar improvements were noticed with nitro-olefins. Nitrostyrene (Entry 7) gave up to 82% ee with L2, a slightly better result than with our previous best ligand L6,[4b] whereas nitrocyclohexene (Entry 8) gave 95% ee with both L2 and L4, the best reported ee for this substrate.

In conclusion, we have shown that the new experimental conditions greatly improve the enantioselectivity of the conjugate addition of dialkyl zincs to several Michael acceptors, and specifically >99% ee for 2-cyclohexenone. Cu$(OTf)_2$ as the copper source could be advantageously replaced by much cheaper copper carboxylates. In addition, we demonstrated that other solvents than toluene are tolerated, a result that may solve the problem of the poor solubility of some substrates. Finally, we have shown that the Lewis acidity of the copper salt, previously believed to play an important role, is not a significant factor.

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Supporting Information Available: Full results on all copper salts, experimental procedures, and analytical data of the conjugate adduct (Chiral GC, SFC, HPLC) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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