Asymmetric Synthesis

Enantioselective Copper-Catalyzed Conjugate Addition to Trisubstituted Cyclohexenones: Construction of Stereogenic Quaternary Centers**

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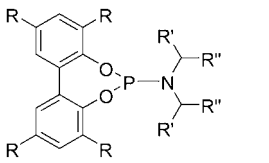
Asymmetric conjugate addition has received increasing interest during the last few years, and excellent results have been obtained, particularly for Cu-[1] and Rh-catalyzed[2] reactions. However, one of the main drawbacks of these two systems is the lack of reactivity of β-trisubstituted enones, thus preventing the formation of chiral quaternary centers.[3]

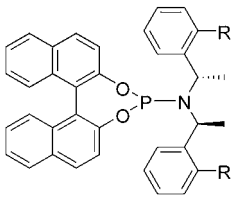
The Cu-catalyzed asymmetric conjugate addition of dialkylzinc reagents has been successfully applied to many substrates, including cyclic[4] and acyclic enones,[4a,b,5] lactones[6] or lactams,[7] nitro olefins,[4b,8] amides,[9] and malonates.[10] However, whatever the Michael acceptor, all reactions with β-trisubstituted substrates failed, probably for steric reasons. Some examples of enantioselective addition of trialkylaluminum reagents have also been described for cyclic[11] and acyclic enones,[12] and nitro olefins.[13] We reasoned that the stronger Lewis acidity of Al would effect a better activation of the substrate than Zn, thus overcoming the inherent steric hindrance of trisubstituted substrates. We report here the success of this approach.

Trialkylaluminum reagents are known to undergo Cu-catalyzed conjugate addition, even with trisubstituted enones.[14] With these reagents stronger coordinating solvents are used than with dialkylzinc reagents (Et_2O or THF instead of toluene or CH_2Cl_2) as this allows the cleavage of the AlR_3 dimeric species, thus increasing its reactivity. We first extensively optimized experimental conditions for the conjugate addition of $AlEt_3$ to 3-methylcyclohexenone, and found that the reaction proceeds to completion after 18 h at −30 °C, and more rapidly at higher temperatures. Two sets of conditions were found, the choice of which depends on the copper salt used: Et_2O is best with copper thiophene carboxylate (CuTC), whereas THF is better with $[Cu(CH_3CN)_4]BF_4$. Although the addition of Me_3SiCl has been reported to increase the chemical yield,[15] we found that it was detrimental in the presence of phosphorus ligands.

In a second step, we screened several biphenol- and binaphthol-based phosphoramidite ligands. The biphenol ligands **L4** (Table 1, entries 4 and 17) and, particularly, **L7** (Table 1, entry 10) afforded the best results in terms of enantioselectivity, whatever the solvent (up to 96.6 % *ee*). In general, the conversions are higher in Et_2O than in THF, although the enantioselectivity is unaffected. Raising the reaction temperature increases the conversion at the cost of a small drop in enantioselectivity (Table 1, entries 4, 5, and 6) from 94 % to 88 % *ee* at −15 °C. The binaphthol ligands **L8**, **L9**, **L10**, and **L11** are less efficient. It should be noted that there is a strong matched/mismatched effect (Table 1, entries 13/14 and 20/21), and that the absolute configuration of the product is dictated by the binaphthol part of the ligand.

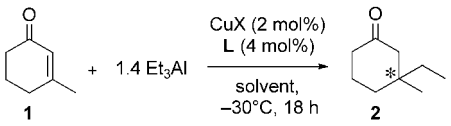


L1 : R=H, R'=Ph, R''=(*S*)-Me
L2 : R=H, R'=Ph, R''=(*R*)-Me
L3 : R=H, R'=Ph, R''=(*R*)-Et
L4 : R=Me, R'=Ph, R''=(*S*)-Me
L5 : R=Me, R'=Ph, R''=(*S*)-Et
L6 : R=H, R'=2-Nph, R''=(*R*)-Me
L7 : R=Me, R'=2-Nph, R''=(*S*)-Me



L8 : (*R, S, S*), R=H
L9 : (*S, S, S*), R=H
L10 : (*R, S, S*), R=OMe
L11 : (*S, S, S*), R=OMe

Table 1: Addition of $AlEt_3$ to 3-methyl-2-cyclohexenone in the presence of various ligands.



Entry	CuX	Ligand	Solvent	Conv. [%]	*ee* [%]	Config.[a]
1	CuTC	**L1**	Et_2O	82	62	*R*
2	CuTC	**L2**	Et_2O	84	62	*S*
3	CuTC	**L3**	Et_2O	46	88	*S*
4	CuTC	**L4**	Et_2O	77	94	*R*
5	CuTC	**L4**	Et_2O[b]	85	90	*R*
6	CuTC	**L4**	Et_2O[c]	>95	88	*R*
7	CuTC	**L4**	THF	15	94	*R*
8	CuTC	**L5**	Et_2O	91	93	*R*
9	CuTC	**L6**	Et_2O	89	78	*S*
10	CuTC	**L7**	Et_2O	>95	96.6	*R*
11	CuTC	**L8**	Et_2O	82	72	*R*
12	CuTC	**L9**	Et_2O	51	62	*S*
13	CuTC	**L10**	Et_2O	>95	74	*R*
14	CuTC	**L11**	Et_2O	>95	16	*S*
15	$[Cu(CH_3CN)_4]BF_4$	**L1**	THF	76	77	*R*
16	$[Cu(CH_3CN)_4]BF_4$	**L3**	THF	46	88	*S*
17	$[Cu(CH_3CN)_4]BF_4$	**L4**	THF	64	94	*R*
18	$[Cu(CH_3CN)_4]BF_4$	**L4**	Et_2O	7	66	*R*
19	$[Cu(CH_3CN)_4]BF_4$	**L7**	THF	<5	n.d.[d]	
20	$[Cu(CH_3CN)_4]BF_4$	**L8**	THF	66	84	*R*
21	$[Cu(CH_3CN)_4]BF_4$	**L9**	THF	65	2	*S*

[a] Product configuration. [b] Reaction was carried out at −25 °C. [c] Reaction was carried out at −15 °C. [d] n.d. = not determined.

In the next step we screened various 3-substituted cyclohexenones (Table 2), which can be easily prepared by a simple protocol from commercially available 3-ethoxycyclohex-

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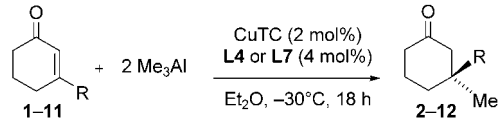
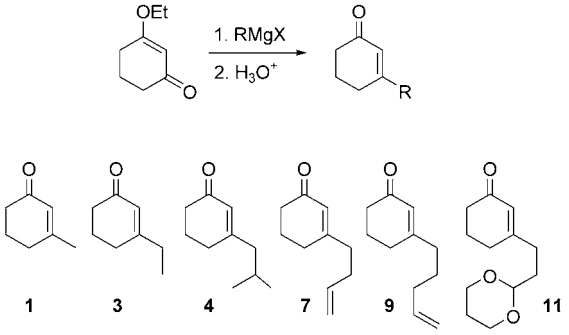
Table 2: Addition of $AlMe_3$ to various 3-substituted cyclohexenones.



Entry	Substrate	Ligand	Adduct	Conv. [%][a]	*ee* [%]	Config.[b]
1	**3**	**L4**	**2**	>95 (78)	94	*S*
2	**3**	**L7**	**2**	84	96	*S*
3	**4**	**L4**	**5**	35	93	*R*
4	**4**	**L7**	**5**	42	93	*R*
5	**7**	**L4**	**8**	>95	91	*R*
6	**7**	**L7**	**8**	>95 (80)	95	*R*
7	**9**	**L4**	**10**	>95	93	*S*
8	**9**	**L7**	**10**	>95 (76)	95	*S*
9	**11**	**L4**	**12**	>95 (81)[c]	95	*R*

[a] Yield of isolated product in parentheses. [b] Product configuration: *R*/*S* notation may change according to the CIP priority rules. [c] 5 mol% CuTC and 10 mol% **L4**.

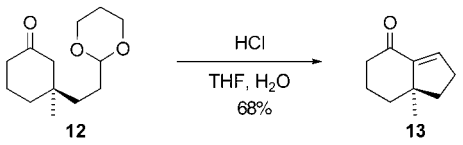
enone (Scheme 1). The addition of $AlMe_3$ to 3-ethylcyclohexenone **3** afforded excellent yields and enantioselectivities, which reached 96% *ee* with **L7** (Table 2, entry 2). As expected, the absolute configuration of the adduct **2** is



Scheme 1. Preparation of 3-substituted cyclohexenones.

opposite to that given in Table 1 (entry 10), thus showing that the face selectivity of the addition remains the same. Although the enantioselectivity remained high (93% *ee*) (Table 2, entries 3 and 4), the addition of $AlMe_3$ to 3-isobutylcyclohexenone **4** proceeded with lower conversion owing to the increased steric demand. In this respect, isophorone **6** did not give any adduct, whereas substrates **7** and **9**, both of which contain a remote double bond, gave excellent yields and enantioselectivities (91 and 93% *ee*, respectively, with **L4**; Table 2, entries 5–8). Finally, an acetal functionality on **11** is tolerated, again with high yield and enantioselectivity (95% *ee*, Table 2, entry 9).

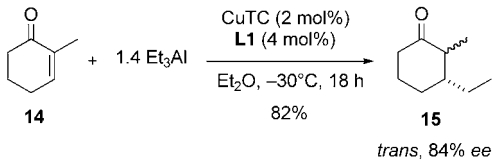
The absolute configuration of the conjugate adducts was determined by chemical correlation with a known compound. Thus, adduct **12**, bearing an acetal functionality, was hydrolyzed and cyclized in situ to afford the bicyclic enone **13** in 68% yield (Scheme 2). The negative optical rotation (−74.6, $c = 1.53$, $CHCl_3$) corresponds to the *R* configuration of **13**.[16] It is assumed that all adducts listed in Table 2 follow the same



Scheme 2. Subsequent hydrolysis of adduct **12** yields the *R*-configured bicyclic enone **13**.

trend. Scheme 2 also illustrates an aspect of the synthetic potential of the above conjugate addition, as such an intramolecular aldol condensation might be applied to the construction of other bicyclic structures.

In addition to 3-substituted cyclohexenones, the 2-substituted analogues are known to be difficult substrates for asymmetric conjugate addition.[1] The present method allows such an extension, again with high yield and good enantioselectivity (84% *ee* for the *trans* isomer and 91% *ee* for the *cis* isomer; Scheme 3). The mixture of *cis* and *trans* isomers of **15** could be equilibrated (DBU, MeOH, room temperature, 20 h) to *trans*/*cis* ratio of 80:20. The *trans* isomer could be isolated in a pure form. The absolute configuration[17] (2*S*,3*R*) shows that the face selectivity remains the same as usual.



Scheme 3. Conjugate addition to 2-substituted cyclohexenones.

In summary, we have discovered a new way to build chiral quaternary centers[18] that allows the straightforward construction of chiral building blocks for more elaborate natural products.

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[18] Typical procedure: A flame-dried Schlenk tube was charged with CuTC (3.9 mg, 2.0 mol%) and **L4** (19.8 mg, 4.0 mol%). Diethyl ether (2.0 mL) was then added and the mixture was stirred at room temperature for 30 min before being cooled to −30 °C. Trimethylaluminum (1.0 mL of a 2 M solution in heptane, 2.0 equiv) was added dropwise at such a rate that the temperature did not rise above −30 °C, and the reaction mixture was stirred at −30 °C for a further 5 min before enone **3** (124.1 mg, 1.0 mmol) in diethyl ether (0.5 mL) was added dropwise. Once the addition was complete the reaction mixture was held at −30 °C overnight. The reaction was quenched at −30 °C by addition of MeOH (0.5 mL) and then water. Workup followed by flash chromatography afforded the product as a colorless oil (109.4 mg, 78% yield). Chiral GC analysis (Lipodex E) showed an enantiomeric excess of 94% *ee*.

