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Copper-Catalyzed Asymmetric Conjugate Addition to α-Alkylidene Cycloalkanones

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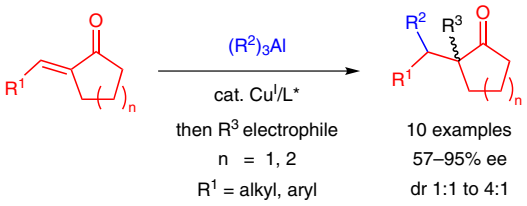

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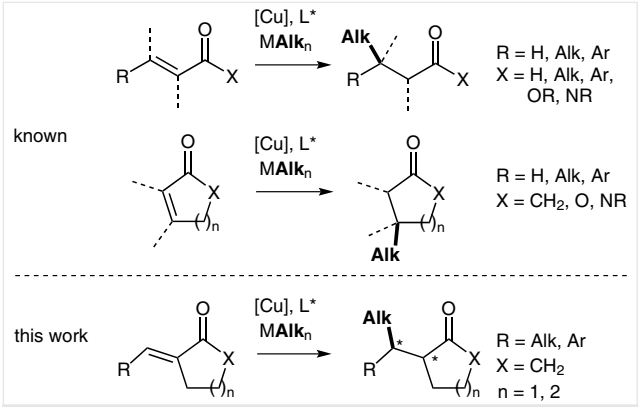
Abstract The asymmetric copper-catalyzed conjugate addition to α-alkylidene cycloalkanones, substituted at their terminal position with aromatic and aliphatic groups, is reported. While high enantioselectivity is reached using chiral phosphoramidite ligands, with R_3Al reagents, moderate diastereoselectivity was observed upon hydrolysis of the aluminium enolates. A Grignard reagent also react with high diastereoselectivity.

Key words α-alkylidene cycloalkanones, conjugate addition, copper, trialkylaluminium reagents, Grignard reagents



Scheme 1 Copper-catalyzed conjugate additions

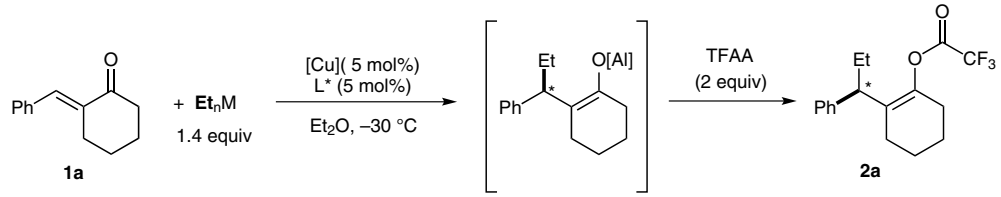
The synthesis of optically active compounds is of prime importance for pharmaceutical needs and is therefore a research field where asymmetric conjugate addition is a key strategy.[1] From a synthetic view point, the use of copper-catalyzed conjugated-addition strategies (Scheme 1) enables the easy introduction of molecular complexity: generation of one or two stereocenters[2] and additional possibilities for further functionalization thanks to the remaining carbonyl group. General approaches for conjugated addition of carbon nucleophiles rely on the use of acyclic or cyclic substrates (Scheme 1, top) and very few approaches for the functionalization of alkylidene cycloalkanones have been reported (Scheme 1, bottom).[3]

Asymmetric conjugate addition of alkyl nucleophiles onto α-alkylidene cycloalkanones have been reported for diastereoselective processes, mainly using a stoichiometric amount of copper.[4,5] An enantioselective version of this transformation employing a catalytic loading of copper salt and chiral ligand would therefore facilitate the synthesis of complex molecules. After a first proof of concept by Woodward in 2001 where the enantioselectivity of the copper-catalyzed addition of diethylzinc onto (*E*)-2-hexylidenecyclopentanone was determined after derivatization, albeit in a rather broad window (72–86% ee),[6] we report herein a specific study devoted to the enantioselective conjugate addition of alkyl nucleophile (Me_3Al, Et_3Al) onto a broad range of α-alkylidene cycloalkanones.

The screening of the reaction conditions (Table 1) consisted of a library of copper salts and chiral ligands, diethyl ether being the preferred solvent as reactions run in THF, dichloromethane, or toluene showed a significant amount of 1,2-addition adduct. In order to gain insights on the enantioselectivity of the transformation, and reduce the number of stereocenters to only one, once the conjugate addition was completed (ca. 2 h), trapping of the resulting enolate was realized with trifluoroacetic acid anhydride and the crude mixture analyzed by chiral GC.

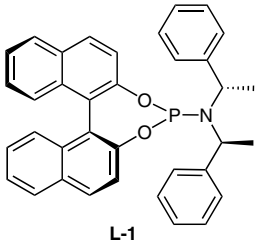
Using ethylmagnesium bromide as nucleophile (Table 1, entries 1–4) did not provide any detectable enantioselectivity, although the conversion toward the expected compound was total.[7] While the use of diethylzinc did not show

Table 1 Optimization of the Reaction Conditions[a]

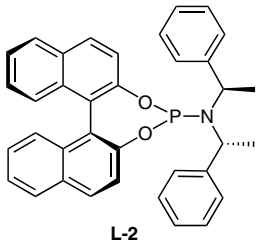


[Cu]	CuCl	CuTc	$[CF_3SO_3Cu]_2{\cdot}C_6H_6$	$Cu(MeCN)_4BF_4$
	Cu-1	**Cu-2**	**Cu-3**	**Cu-4**

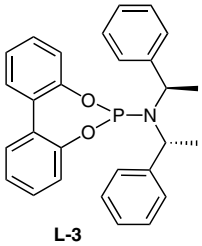
L*



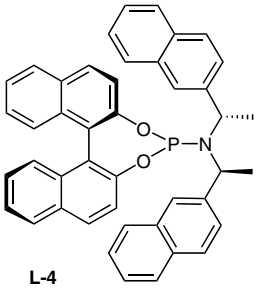
L-1



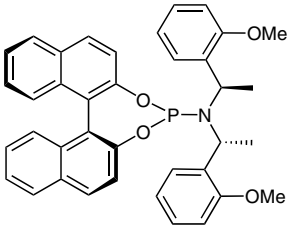
L-2



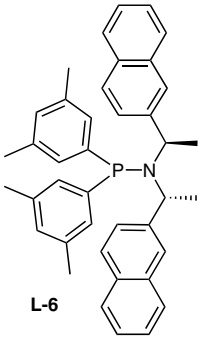
L-3



L-4



L-5



L-6

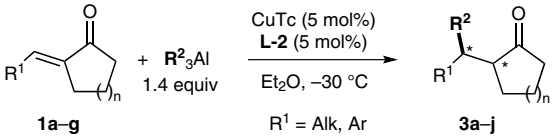
Entry	[Cu]	L*	Et_nM	ee[b,c]
1	**Cu-1**	**L-1**	EtMgBr	0
2	**Cu-1**	**L-2**	EtMgBr	0
3	**Cu-2**	**L-2**	EtMgBr	0
4	**Cu-3**	**L-1**	EtMgBr	0
5	**Cu-4**	**L-1**	Et_2Zn	0
6	**Cu-3**	**L-1**	Et_3Al	56
7	**Cu-4**	**L-1**	Et_3Al	33
8	**Cu-2**	**L-1**	Et_3Al	67
9	**Cu-2**	**L-2**	Et_3Al	84
10	**Cu-2**	**L-3**	Et_3Al	55
11	**Cu-2**	**L-4**	Et_3Al	–77
12	**Cu-2**	**L-5**	Et_3Al	70
13	**Cu-2**	**L-6**	Et_3Al	4

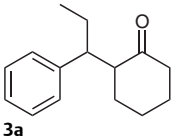
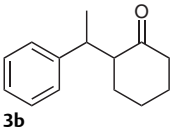
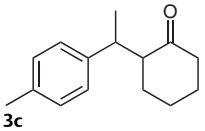
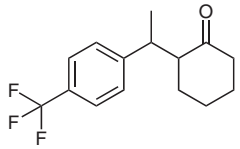
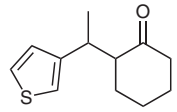
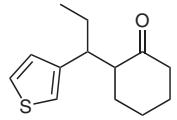
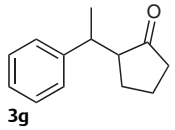
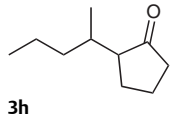
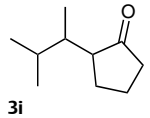
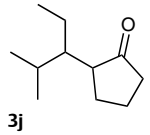
[a] Reaction conditions: **1a** (0.27 mmol), Et_nM (0.37 mmol), CuTc (0.013 mmol), **L*** (0.013 mmol), Et_2O (3 mL).
[b] Full conversion in all cases; determined by GC.
[c] Determined by chiral GC on **2a**.

any improved conditions (Table 1, entry 5), switching to triethylaluminium provided an initial enantioselective conjugate addition example (56% ee, Table 1, entry 6). In accord with literature suggestions, copper thiophene-2-carboxylate (CuTc) was identified as the best copper catalyst after further evaluation (Table 1, entries 7 and 8).[8] With the appropriate catalyst in hand, the last parameter screened was the influence of the ligand. A remarkable improvement was reached using the diastereoisomer of ligand **L-1**: **L-2** provided a high enantioselectivity of 84% enantiomeric excess (Table 1, entry 9).[9] Removal of the chirality at the aryloxy backbone (**L-3**) or the use of bulkier aryl groups at the amido part of the phosphoramidite ligand **L-4** were detrimental with 55% and 77% enantiomeric excess, respectively (Table 1, entries 10 and 11). Finally, use of related **L-5**, with *o*-methoxy group, did not yield improved conditions (Table 1, entry 12) while the use of the phosphanamine **L-6** afforded almost a racemate (Table 1, entry 13).[10]

Having determined our best conditions (Table 1, entry 9), the scope of application of this procedure was evaluated (Table 2) using trimethylaluminium and triethylaluminium as nucleophiles and a broad range of α-alkylidene cyclohexanones or cyclopentanones substituted with either aromatic or aliphatic groups. As we were most interested in reaching functionalized cycloalkanones, quench of the reaction mixture was realized using 1.2 M HCl in MeOH.

Table 2 Substrate Scope[a]



Entry	R^1	n	R^2	Product	dr[b]	ee[c]
1	Ph	2	Et	 **3a**	1.3:1	84
2	Ph	2	Me	 **3b**	2.1:1	90
3	4-MeC_6H_4	2	Me	 **3c**	1.7:1	95
4	4-$F_3CC_6H_4$	2	Me	 **3d**	2.2:1	92
5	3-thienyl	2	Me	 **3e**	3.1:1	82
6	3-thienyl	2	Et	 **3f**	1.2:1	68
7	Ph	1	Me	 **3g**	2.3:1	57
8	*n*-Pr	1	Me	 **3h**	2:1	94
9	*i*-Pr	1	Me	 **3i**	4.2:1	94
10	*i*-Pr	1	Et	 **3j**	1:1	77

[a] Reaction conditions: **1a–g** (0.27 mmol), $AlAlk_3$ (0.37 mmol), CuTC (0.013 mmol), **L-2** (0.013 mmol), Et_2O (3 mL)
[b] Full conversion in all cases; determined by GC.
[c] Determined by chiral GC.

When the optimal reaction conditions of Table 1 were used, a diastereomeric ratio of 1.3:1 (Table 2, entry 1) was obtained. Interestingly, using Me_3Al instead of Et_3Al allowed access to a higher enantioselectivity of 90% enantiomeric excess and a rather increased diastereoselectivity of 2.1:1 (Table 2, entry 2). In both cases, the enantioselectivity of the two diastereomers was identical, showing that the protonation of the enolates is not affected by the chiral ligand. Keeping Me_3Al as the nucleophile, the influence of the substitution at the *para* position was briefly studied. Thus, either 4-Me (95% ee, 1.7:1 dr) or 4-CF_3 (92% ee, 2.2:1 dr) groups furnished the target product in similar enantio-

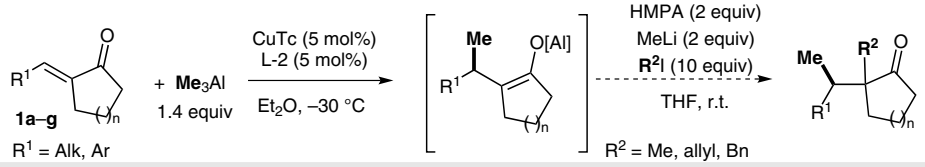
selectivity and diastereoselectivity to **3b** (Table 2, entries 3 and 4). After the evaluation of the influence of the aromatic group at the alkene terminus, the influence of an heteroaromatic group was studied using a 3-thienyl group. As for previous cases, higher enantioselectivity and diastereoselectivity was observed when Me_3Al was used instead of Et_3Al (Table 2, entries 5 and 6). Notably, here the presence of a sulfur atom interfered only slightly with the reaction performance as the enantioselectivity of 82% reached for **3e**[11] remained high.

Contracting the cyclohexanone framework to cyclopentanone, the enantioselectivity of the addition of Me_3Al dropped dramatically from 90% to 57% (Table 2, entries 2 vs. 7) while a similar diastereoselectivity (2.1:1 vs. 2.3:1) was attained. Gratifyingly, in the presence of an alkyl terminus, instead of the aromatic one previously discussed, an excellent enantiomeric excess of 94% was reached even though a low diastereomeric ratio of 2:1 was still observed (**3h**, Table 2, entry 8). Changing from *n*-Pr to *i*-Pr group yielded **3i**[12] with the same enantioselectivity of 94% but pleasingly with a higher diastereoselectivity of 4.2:1 (Table 2, entry 9). Again, the use of Et_3Al furnished **3j** with lower enantiomeric excess and diastereomeric ratio (entry 10).

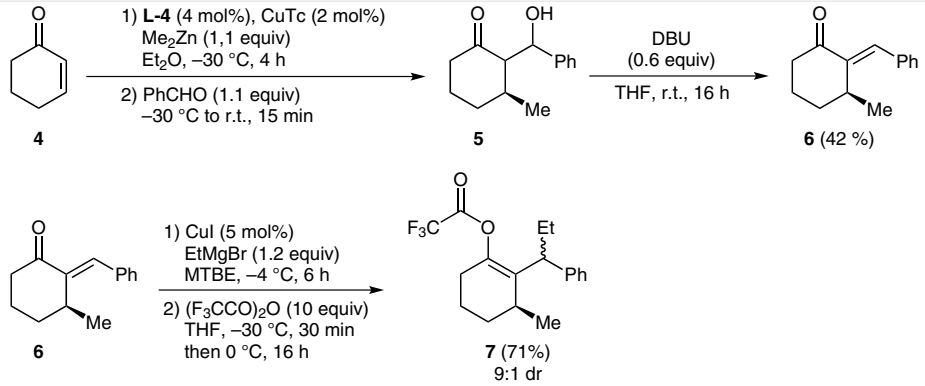
While the addition of Me_3Al enabled very high enantioselectivities to be reached, simple hydrolysis of the transient enolate furnished a tertiary center with only modest diastereoselectivity. Therefore, we questioned whether the use of other electrophiles than TFAA (Table 1) or H^+ (Table 2) would provide greater stereoselection at the quaternary center through C-alkylation (Scheme 2).[13] After optimization, reaction conditions close to those reported by Cramer[14] were identified: requirement of additional HMPA and MeLi in THF along with reactive electrophiles such as methyl iodide, allyl iodide, or benzyl iodide.

Unfortunately, the trapping reaction, generating the quaternary center α to the tertiary center built during the nucleophilic attack, showed very poor reproducibility. Indeed, despite extended efforts to optimize this step, variable and significant amounts of the product from simple hydrolysis were always present in the crude mixture.[15] We reasoned that this could arise from enolate equilibration between the transient enolate and the final compound. Notwithstanding this drawback, the diastereoselectivity of the trapping was reproducible. However, as this was rather low, similar to those observed during the direct hydrolysis of the transient aluminium enolate (max. 3:1), we did not pursue this investigation.

We eventually studied the influence of a stereogenic center onto the substrate (Scheme 3). We anticipated, based on literature precedent, that substituting the cycle may have an effect on the outcome of the title reaction.[4,5] For example, asymmetric conjugate addition of dimethylzinc to **4** followed by zinc enolate trapping with benzaldehyde and subsequent elimination afforded **6** in 42% isolated yield after three steps, and >99% enantiomeric excess.[16,17] We therefore attempted different catalytic systems but none of them was as reactive except copper iodide promoted 1,4-addition of Grignard reagents. Starting from a racemic mixture of **6**, we managed to isolate a mixture of diastereomers of **7** in 88:12 diastereomeric ratio. The same ratio was observed after reaction with enantiomerically pure unsaturated ketone **6**: only one enantiomer of each diastereomer



Scheme 2 Attempted C-alkylation of the transient aluminium enolate



Scheme 3 Conjugate addition to chiral substrates

was observed (90:10 dr). Even if we were not able to deduce the absolute configuration of the new stereogenic carbon, the presence of a stereodefined tertiary center at this position lead to a diastereoselective conjugate addition to proximal *exo*-methylanated ketones. The development of a new catalyst could allow us to study match and mismatch cases associated to the asymmetric conjugate addition to enantiopure unsaturated ketones. Furthermore, the synthesis of **7** was a model considered en route to more complex systems. Indeed, we could trap the magnesium enolate with allyl chloroformate and thus prepare the corresponding allyl enol carbonate (not shown). By looking at the palladium-catalyzed decarboxylative allyl alkylation[18] for this system and the different catalyst–substrate combination, we would have access to three contiguous stereogenic centers.

In conclusion, we have developed a general method for the enantioselective conjugate addition of trialkylaluminium reagents onto α-alkylidene cycloalkanones using CuTc as catalyst and phosphoramidite ligand **L-2**. Trimethylaluminium provides better enantioselectivity than triethylaluminium (up to 95% ee). α-Alkylidene cyclohexanones and cyclopentanones are suitable substrates and these can be substituted with the olefin termini being aromatic, heteroaromatic, or alkyl groups. While the nucleophilic addition is stereocontrolled, trapping of the transient aluminium enolate showed a low diastereoselectivity using either H^+ or alkylating reagent. Further development for such transformation would therefore overcome the observed limitation for the diastereoselectivity as well as direct use in the synthesis of biorelevant targets.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380165.

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(11) **General Procedure**
In a Schlenk tube, to a solution of α-alkylidene cyclohexanone **1d** (51.5 mg, 0.27 mmol), CuTc (2.5 mg, 0.013 mmol), **L-2** (7.0 mg, 0.013 mmol) in Et_2O (3 mL) at –30 °C was added dropwise a solution of Me_3Al (2.0 M in heptane, 188 µL, 0.37 mmol), and the reaction was stirred for 2 h. At this point, an aliquot was taken and quenched with Ac_2O to determine the enantioselectivity. After addition of 2 mL of 1.2 M HCl in MeOH the reaction was stirred at r.t., and a saturated solution of Rochelle's (or Seignette) salt was added (5 mL). After extraction of the aqueous phase with Et_2O, the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. GC analysis was used to determine the conversion and purification on silica gel (cyclohexane–EtOAc, 99:1) afforded **3e** as colorless oil in 70% yield. Mixture of diastereomers = 3.1:1; dias indicates signals due to both. ^1H NMR (400 MHz, $CDCl_3$): δ

= 1.14–1.23 (m, 4.5 H, 2 dias), 1.44–1.53 (m, 1.5 H, 2 dias), 1.59–1.73 (m, 3.1 H, 2 dias), 1.78–1.98 (m, 1.7 H, 2 dias), 2.15–2.38 (m, 3.1 H, 2 dias), 2.43–2.48 (m, 1 H, dia minor), 3.26–3.34 (m, 1 H, dia major), 3.47–3.53 (m, 1 H, dia minor), 6.86–6.89 (m, 2 H, 2 dias), 7.15–7.18 (m, 1 H, 2 dias). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 20.7, 24.3, 24.9, 27.7, 28.2, 28.4, 31.9, 32.9, 34.2, 42.2, 42.3, 56.5, 57.7, 119.9, 120.6, 125.2, 125.4, 127.2, 127.5, 145.6, 146.9, 211.9, 213.3. IR (ATR): 3100, 2936, 2867, 1705, 1450, 1129, 785 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{12}H_{16}OS$: 208.09164; found: 208.09173.

(12) **3i**: Colourless oil. Mixture of diastereomers = 4.2:1. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.71 (d, *J* = 6.9 Hz, 1 H, dia minor), 0.81 (d, *J* = 6.8 Hz, 3 H, dia major), 0.85 (d, *J* = 6.8 Hz, 3 H, dia major), 0.90 (d, *J* = 6.7 Hz, 2 H, dia minor), 0.93 (d, *J* = 6.9 Hz, 3 H), 1.49–1.55 (m, 1.3 H, 2 dias), 1.61–1.81 (m, 4.3 H, 2 dias), 1.93–2.03 (m, 3.2 H, 2 dias), 2.05–2.13 (m, 1.9 H, 2 dias), 2.18–2.29 (m, 1.7 H, 2 dias). ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 13.4, 13.7, 18.3, 20.5, 21.1, 21.2, 21.3, 22.0, 24.7, 28.2, 30.4, 32.2, 38.8, 39.4, 39.6, 39.7, 52.6, 53.7, 220.0 (dia major), 221.7 (dia minor). IR (ATR): 2960, 2875, 1734, 1464, 1150 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{10}H_{18}O$: 154.13522; found: 154.13513.

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