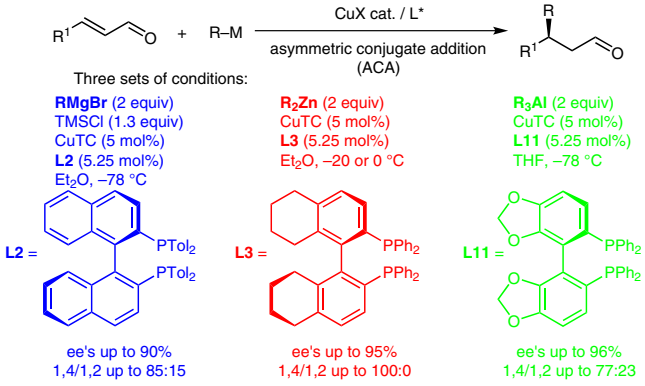
Synthesis S. Goncalves-Contal et al. Paper

Copper-Catalyzed Enantioselective Conjugate Addition to α,β-Unsaturated Aldehydes with Various Organometallic Reagents

Sylvie Goncalves-Contal
Ludovic Gremaud
Laëtitia Palais
Lucille Babel
Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, 1211 Geneva 1211, Switzerland
alexandre.alexakis@unige.ch

Dedicated to the memory of Professor Jean F. Normant (1936–2016)

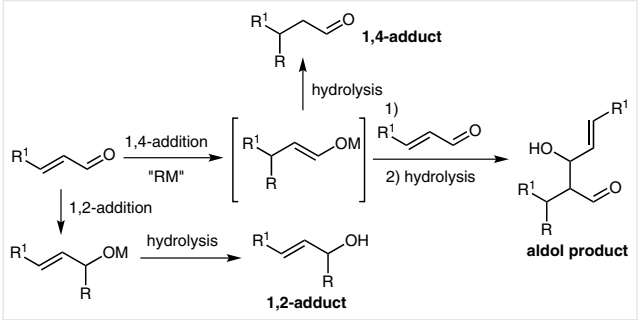


Received: 19.04.2016
Accepted after revision: 20.05.2016
Published online: 28.06.2016
DOI: 10.1055/s-0035-1562487; Art ID: ss-2016-c0260-op

Abstract β-Substituted aldehydes constitute a very important class of compounds found in nature. Synthesis of this motif can be envisioned by C–C bond formation on enals. For this purpose, we report herein the development of enantioselective copper-catalyzed conjugate addition of various organometallic reagents to α,β-unsaturated aldehydes with (*R*)-H_8BINAP, (*R*)-TolBINAP, and (*R*)-SEGPHOS as chiral ligands. Three sets of conditions were successfully developed and several enals were used. Reactivity and regio- and enantioselectivities were strongly dependent on reaction conditions and substrates. Good to excellent regio- and enantioselectivities were obtained with zinc reagents R_2Zn and aluminum reagents R_3Al. However, the asymmetric conjugate addition of Grignard reagents afforded only moderate to good regio- and enantioselectivities.

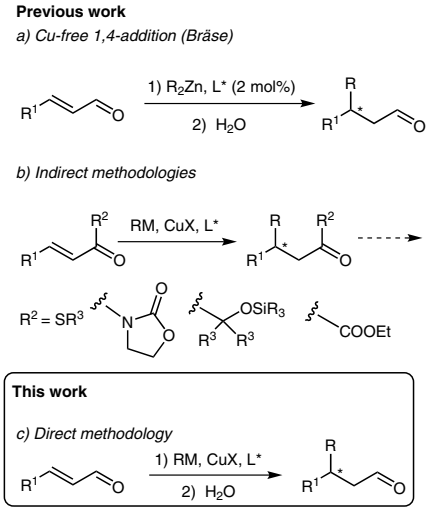
Key words α,β-unsaturated aldehydes, conjugate addition, organometallic reagents, enantioselectivity, natural products

Among the different methodologies reported to create carbon–carbon bonds in an enantioselective manner, asymmetric copper-catalyzed conjugate addition (ACA) of organometallic reagents to Michael acceptors is one of the most powerful.[1] As a consequence, several α,β-unsaturated compounds were developed successfully, such as carbonyl derivatives, sulfones, or nitroalkenes. Among all the classes of Michael acceptors, α,β-unsaturated aldehydes appear to be the most interesting ones, as the 1,4-addition to such compounds results in the formation of important β-alkyl-substituted chiral molecules having interesting properties or being key synthons for the preparation of natural products. However, nowadays, the direct enantioselective conjugate addition to α,β-unsaturated aldehydes still remains a challenge in terms of regio- and enantioselectivity, with few examples reported so far. Due to their high reactivity, direct addition to the carbonyl could occur and lead to the 1,2-adduct as byproduct (Scheme 1). The intermediate enolate could also react with the highly reactive enal to give the aldol product as the second possible byproduct. In 2005, Bräse highlighted the problem when he reported the enantioselective copper-free 1,4-addition of diorganozinc to α,β-unsaturated aldehydes (Scheme 2 a).[2] By using [2.2]paracyclophaneketimine ligands, excellent enantioselectivities were attained but these were counterbalanced by low regioselectivities (with1,4/1,2 ratios between 4:1 and 1:1).



Scheme 1 Regioselectivity in the ACA of organometallics to enals

One year later, Marshall described the silyl-promoted copper-catalyzed 1,4-addition of organozinc reagents to enals with a cyanocuprate as catalyst.[3] Here, 1,4-adducts were obtained as the sole product in racemic and diastereoselective manners. Recently, Córdova described the enantioselective 1,4-addition of a dimethylsilyl group to α,β-unsaturated aldehydes.[4] Combining copper activation of the nucleophile and chiral aminocatalysis allowed exclusive 1,4-selectivity with moderate to good enantioselectivities. Finally, rhodium[5] and palladium[6] were also reported as possible transition metal catalysts in the asymmetric conjugate



Scheme 2 Strategy developed in this article

addition to enals of arylboronic acid, arylzinc chloride, and triarylbismuth. With all these chiral systems, only β-aryl-substituted aldehydes could be obtained. Moreover, in copper and copper-free systems, the scope of the nucleophiles seemed to be one of the limitations (apart from 1,4-selectivity) as only organozinc and silyl reagents were described.

With the aim of efficiently accessing β-substituted chiral aldehydes, indirect pathways were developed where the 1,4-adduct could easily be converted into the corresponding aldehydes. These strategies dealt with the copper-catalyzed conjugate addition to *N*-acyloxazolidinones,[7] thioesters,[8] α′-silyloxy enones,[9] α-chloroallylic acetates,[10] or, more recently, 2*H*-pyran-2-one[11] and keto esters[12] (Scheme 2 b). However, there was still a need for a direct asymmetric conjugate addition to α,β-unsaturated aldehydes for the sake of ease, speed, and atom-economic processes. The lack of such an efficient and general direct methodology prompted us to report in 2010 the first asymmetric copper-catalyzed conjugate addition of organozinc and Grignard reagents to enals, giving rise to the desired 1,4-adducts in moderate to good regio- and enantioselectivities.[13] Focusing our efforts on this topic, herein, we present our plentiful experience in this field as well as our recent progress to enhance regio- and enantioselectivities in the copper-catalyzed 1,4-addition to enals with various organometallic reagents (R_2Zn, RMgBr, and R_3Al) and using commercially available bidentate ligands and copper salts.

We first envisioned the ACA to enals by using dialkylzinc reagents. Indeed, diorganozinc reagents are less reactive than the corresponding organomagnesium and triorganoaluminum ones. Several functional groups on the substrates as well as on the organozinc itself are well tolerated.[14] Therefore, we assumed that they may prevent or slow down 1,2-addition compared to other organometallic reagents. Ligands used in all the following studies are depicted in Figure 1: mainly di- and monophosphorylated binaphthyl-type ligands (**L1**–**L4**), SYNPHOS and SEGPHOS derivatives (**L6**–**L14**) and ferrocene-type ligands (**L17** and **L18**).[15]

Asymmetric Cu-Catalyzed Conjugate Addition of R_2Zn to Enals

Conjugate addition of diethylzinc to *trans*-2-decenal (**S1**) was first studied in order to access 1,4-adduct **A1** exclusively (Table 1). Previously, we described that using (*R*)-BINAP (**L1**) as ligand gave only 1,4-addition with a promising enantiomeric excess of 75% (entry 1).[13] However, the reaction could be further improved in terms of enantioselectivity, and thus we focused on screening the chiral ligand. Among binaphthyl derivatives, (*R*)-H_8BINAP (**L3**) allowed the exclusive conjugate addition to adduct **A1** with a very good *ee* of 95% (entry 3). No traces of 1,2-adduct or aldol product were observed. When SYNPHOS derivatives were tested, only (*R*)-SYNPHOS (**L6**) was efficient, providing **A1** with a 1,4/1,2 ratio of 95:5 and a good *ee* of 92% (entry 6).

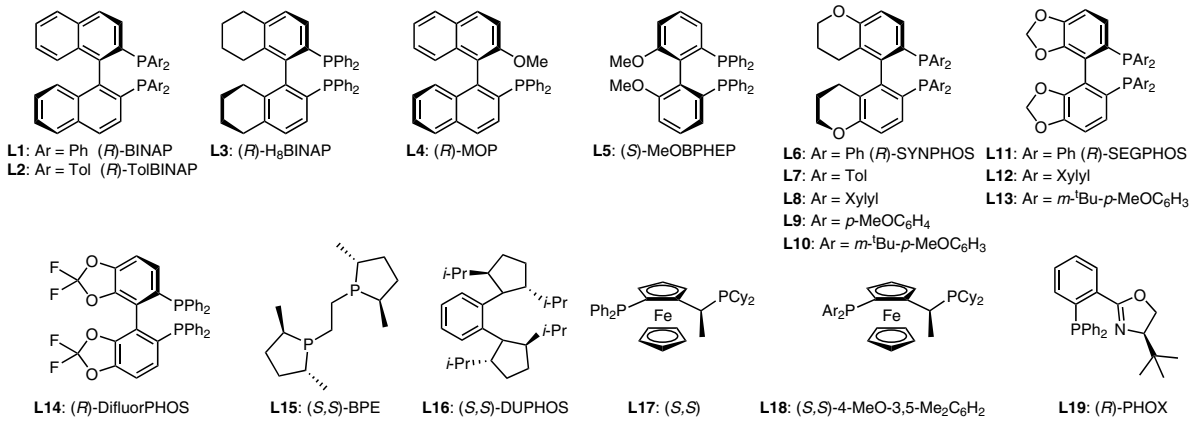
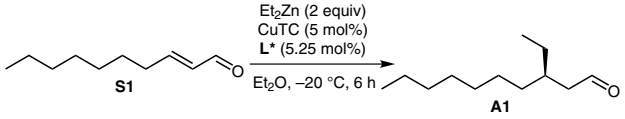


Figure 1 Chiral ligands used in this study

The enantiomeric excess also decreased when the steric hindrance on the ligand increased (entries 6–10). Indeed, the excess dropped from 92 to 22% going from **L6**, with phenyl on the phosphorus atoms, to **L10** with 3-*tert*-butyl-4-methoxyphenyl substituents. Finally, no improvements were observed by using **L11** to **L14** from the SEGPHOS family or ferrocene-type ligands (entries 11–14, 17, and 18).

Table 1 Screening of Ligands for the ACA of Diethylzinc to *trans*-Decenal

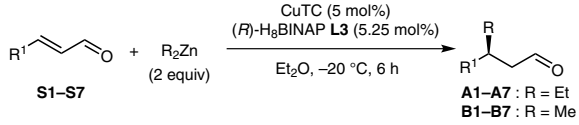


Entry	Ligand **L***	Conv. (%)[a]	Ratio 1,4/1,2/aldol	*ee* (%)[b]
1	**L1**	100	100:0:0	75
2	**L2**	84	79:21:0	67
3	**L3**	100	100:0:0	95
4	**L4**	95	71:29:0	10
5	**L5**	88	82:18:0	65
6	**L6**	100	95:5:0	92
7	**L7**	90	76:18:6	86
8	**L8**	95	69:24:7	80
9	**L9**	85	61:32:7	78
10	**L10**	95	71:18:11	22
11	**L11**	98	100:0:0	84
12	**L12**	91	86:14:0	75
13	**L13**	85	100:0:0	29
14	**L14**	98	90:10:0	58
15	**L15**	80	84:0:16	11
16	**L16**	87	66:0:34	9
17	**L17**	87	100:0:0	78
18	**L18**	87	69:0:31	57
19	**L19**	100	85:0:15	23

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by chiral GC.

Having identified (*R*)-H_8BINAP as the best ligand for the conjugate addition of diethylzinc to *trans*-2-decenal (**S1**), these optimal conditions were next applied to various α,β-unsaturated aldehydes (Table 2). In almost all cases, the enantiomeric excesses obtained with (*R*)-H_8BINAP were higher than the ones previously described[13] using (*R*)-BINAP. Concerning the conjugate addition of Et_2Zn, small and long primary alkyl chains gave excellent results with perfect regioselectivity and very high *ee* between 81 and 95% for the addition of Et_2Zn (entries 1–4 and 6). Due to its lower reactivity, addition of Me_2Zn must be run at 0 °C to get complete conversion and 1,4-adducts bearing primary alkyl chains **B1**, **B2**, **B3** and **B6** were obtained with lower *ee* between 59 and 78% (entries 8–10 and 13). Conjugate addition was more difficult with enals bearing a phenyl or secondary alkyl group in β-position (entries 4, 5, 7, 11, 12, and 14). Indeed, unsatisfactory 1,4/1,2/aldol ratios were obtained even though the *ee*'s were good. The only exception is the conjugate addition of Et_2Zn to isopropyl enal **A4** with an excellent 1,4/1,2 ratio and a very good 91% *ee* (entry 4).

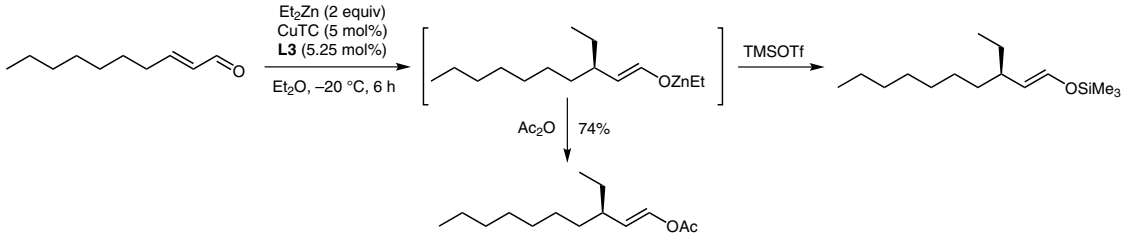
Table 2 ACA of Dimethylzinc and Diethylzinc to Various Enals



Entry	R^1	Adduct	Conv. (%)[a]	Ratio 1,4/1,2	*ee* (%)[b]
1	$(CH_2)_6Me$	**A1**	100 (77)[c]	100:0	95 (75)[d]
2	*n*-Bu	**A2**	100 (58)[c]	100:0	92 (64)[d]
3	*i*-Bu	**A3**	100	100:0	89 (70)[d]
4	*i*-Pr	**A4**	100 (46)[c]	100:0	91[e] (70)[d]
5	Cy	**A5**	100 (23)[c]	31:69	78 (52)[d]
6	$(CH_2)_2Ph$	**A6**	100 (74)[c]	100:0	81
7	Ph	**A7**	100	62:0:38[g]	71 (44)[d]
8[f]	$(CH_2)_6Me$	**B1**	100	100:0	78 (68)[d]
9[f]	*n*-Bu	**B2**	100	100:0	76 (76)[d]
10[f]	*i*-Bu	**B3**	100	100:0	59
11[f]	*i*-Pr	**B4**	100	44:0:56[g]	81 (70)[d]
12[f]	Cy	**B5**	100	31:69	58 (60)[d]
13[f]	$(CH_2)_2Ph$	**B6**	100	65:0:35[g]	78
14[f]	Ph	**B7**	100	32:68	62 (64)[d]

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by chiral GC.
[c] Value in parentheses is the isolated yield determined after reduction to the corresponding alcohol. Due to the volatility of some alcohols, some isolated yields are lower.
[d] Value in parentheses is the previous *ee* reported by our group.[13]
[e] The *ee* of the corresponding alcohol after reduction.
[f] Reaction carried out at 0 °C.
[g] Ratio 1,4/1,2/aldol.

Finally, we determined the stereochemistry of the intermediate enolate by trapping experiments providing the silyl enol ether[16] or the enol acetate[17] (Scheme 3). In both cases, *E* compounds were obtained. Thus, conjugate addition to enals proceeded through the *s-trans* conformation, giving the *E*-enolate.



Scheme 3 Enolate trapping experiment

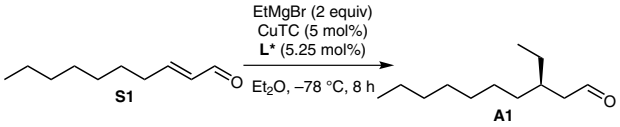
Asymmetric Cu-Catalyzed Conjugate Addition of RMgBr to Enals

Grignard reagents seem more interesting than diorganozincs if we consider commercial diversity. This is why we envisioned them in the conjugate addition to enals, and first to *trans*-decenal **S1** (Table 3). Due to their higher reactivity, regioselectivity may be more difficult to control leading to complex mixtures of 1,4- and 1,2-adducts as well as aldol products. For this reason, the reactions were carried out at –78 °C and gave excellent conversions in almost all cases. (*R*)-BINAP (**L1**) and (*R*)-TolBINAP (**L2**) were first tested using CuTC [copper(I) 2-thiophenecarboxylate] as catalyst and EtMgBr (entries 1 and 2). However, good enantioselectivities (around 90%) were counterbalanced by low regioselectivities. By adding TMSCl (trimethylchlorosilane), it was possible to reach a good 1,4/1,2 ratio of 85:15 along with 90% *ee*, with **L2** as ligand (entry 3). Several bidentate ligands were then considered to enhance the regio- and enantioselectivities. (*R*)-SYNPHOS (**L6**) gave a quite similar 1,4/1,2 ratio but with a lower *ee* of 67% (entry 5). Finally, almost only the 1,2-adduct was obtained when (*R*)-SEGPHOS derivatives or ferrocene-type ligands were used (entries 6–11).

As shown above, adding TMSCl was crucial to access satisfactory regioselectivity. Indeed, since the pioneering work of Normant,[18] TMSCl has been known to promote 1,4-addition to enals. It also increases the rate of conjugate addition of the cuprate.[19] In an effort to further improve these results, various halosilanes were investigated in the conjugate addition (Table 4). We hypothesized that a more reactive silane would trap the enolate faster, increasing the rate of reductive elimination and thus favor the 1,4-addition. Unfortunately, this was not the case, as raising reactivity favored the 1,2-process (entries 2–4). TMSOTf was even too reactive, leading to complete degradation of the enal (entry 5). The last attempts to improve regioselectivity consisted of testing other solvents with TMSCl as additive. Neither toluene, nor CH_2Cl_2, nor MeTHF (2-methyltetrahydrofuran) gave better results than Et_2O (entries 6–8). In all the cases, 1,2-addition was preferred.

The best conditions for the conjugate addition of Grignard reagents to enals were thus identified: CuTC as catalyst, (*R*)-TolBINAP (**L2**) as ligand, and TMSCl as additive in Et_2O at –78 °C. We next applied them to various enals in the reaction with EtMgBr (Table 5, entries 1–7). Enals bearing a primary alkyl group in the β-position (**S1**, **S2**, **S3**, and **S6**) provided the best *ee*'s (up to 90%) with the 1,4-regioselectivity from 71 to 85% (entries 1–3 and 6). As a general trend, the regioselectivity remains moderate despite the benefit provided by TMSCl. A decrease of the chiral induction was observed for substrates having a secondary alkyl moiety (entries 4 and 5). Finally, the use of cinnamaldehyde **S7** resulted in an important drop both in terms of regio- and enantioselectivity (entry 7). Then the addition of a methyl group in β-position was investigated by employing MeMgBr as Grignard reagent (entries 8–13). In all cases, both 1,4-regio- and enantioselectivity were inferior, except for the phenethyl-substituted **S6**. The latter gave 1,4-adduct **B6** with a slightly better *ee* of 88% (entry 12). It has to be noted that **B6** is a floral fragrance called Citralis®.

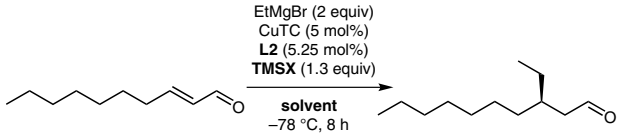
Table 3 Optimization of the ACA of Ethylmagnesium Bromide to *trans*-Decenal



Entry	Ligand **L***	Additive	Conv. (%)[a]	Ratio 1,4/1,2/aldol	*ee* (%)[b,c]
1	**L1**	–	98	62:38:0	89
2	**L2**	–	99	32:42:26	92
3	**L2**	TMSCl	100	85:15:0	90
4	**L3**	TMSCl	96	38:56:6	86
5	**L6**	TMSCl	84	79:21:0	67
6	**L11**	TMSCl	95	4:96:0	n.d.
7	**L12**	TMSCl	98	3:97:0	n.d.
8	**L13**	TMSCl	95	13:82:5	70
9	**L14**	TMSCl	94	18:82:0	86
10	**L17**	TMSCl	87	8:86:6	n.d.
11	**L18**	TMSCl	86	24:76:0	87

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by chiral GC.
[c] n.d. = not determined.

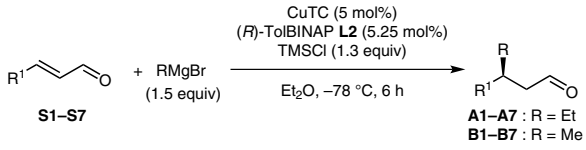
Table 4 Influence of the Halosilane Additive and the Solvent



Entry	TMSX	Solvent	Conv. (%)[a]	Ratio 1,4/1,2[a]	*ee* (%)[b,c]
1	TMSCl	Et_2O	100	85:15	90
2	TMSBr	Et_2O	100	43:57	90
3[d]	TMSI	Et_2O	60	10:90	4
4[d]	TMSCN	Et_2O	94	7:93	n.d.
5[d]	TMSOTf	Et_2O	100[e]	n.d.	n.d.
6	TMSCl	toluene	100	2:98	77
7	TMSCl	CH_2Cl_2	100	43:57	70
8	TMSCl	MeTHF	95	16:84	56

[a] Conversion (conv.) was determined by ^{1}H NMR spectroscopy.
[b] The *ee* was determined by chiral GC.
[c] n.d. = not determined.
[d] TMSX was added at –78 °C to the copper complex, followed by *trans*-decenal 20 min thereafter.
[e] Complete degradation of the enal.

Table 5 ACA of Methylmagnesium Bromide and Ethylmagnesium Bromide to Various Enals

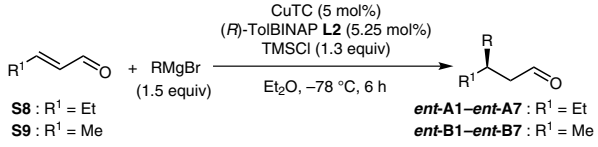


Entry	R^1	Adduct	Conv. (%)[a]	Ratio 1,4/1,2	*ee* (%)[b,c]
1	$(CH_2)_6Me$	**A1**	100 (75)[d]	85:15	90
2	*n*-Bu	**A2**	100 (46)[d]	60:40	90
3	*i*-Bu	**A3**	100 (44)[d]	71:21	90
4	*i*-Pr	**A4**	100	36:64	74
5	Cy	**A5**	100 (51)[d]	63:37	80
6	$(CH_2)_2Ph$	**A6**	100 (59)[d]	77:23	83
7	Ph	**A7**	100	20:80	53
8	$(CH_2)_6Me$	**B1**	100 (40)[d]	65:35	81
9	*n*-Bu	**B2**	100	40:60	86
10	*i*-Pr	**B4**	86	43:57	84
11	Cy	**B5**	100 (49)[d]	63:37	77
12	$(CH_2)_2Ph$	**B6**	97	48:52	88
13	Ph	**B7**	100	10:90	n.d.

[a] Conversion (conv.) was determined by ^{1}H NMR spectroscopy.
[b] The *ee* was determined by chiral GC.
[c] n.d. = not determined.
[d] Isolated yield given parentheses.

Lastly, various Grignard reagents were added to *trans*-2-pentenal (**S8**) and crotonaldehyde (**S9**), with the aim of getting the enantiomers of the 1,4-adducts obtained previously by addition of EtMgBr and MeMgBr (Table 6). Concerning the conjugate addition to **S8**, three 1,4-adducts have a better *ee* than their corresponding enantiomers obtained previously by addition of EtMgBr. Cyclohexylmagnesium bromide gave access to the adduct *ent*-**A5** with 86% *ee*, however with lower regioselectivity compared to **A5**, obtained in 80% *ee* and a 1,4/1,2 ratio of 63:37 (Table 5, entry 5 vs Table 6, entry 3). Secondly, the addition of phenethylmagnesium bromide to **S8** took place in 88% *ee* and a 1,4/1,2 ratio of 67:33, whereas the addition of EtMgBr to **S6** proceeded in 83% *ee* and a 1,4-regioselectivity of 77% (Table 6, entry 4 vs Table 5, entry 6). A great improvement was finally obtained by addition of phenylmagnesium bromide. The *ee* increased from 53 to 80% but, still, with a low 1,4-regioselectivity (Table 6, entry 5 vs Table 5, entry 7). For the conjugate addition to an enal bearing a methyl in β-position **S9**, cyclohexylmagnesium bromide gave the best result: 1,4-adduct *ent*-**B5** was obtained in 89% *ee* and a 1,4-regioselectivity of 71% (Table 6, entry 8). Both the regio- and enantioselectivity were better than the ones observed for the addition of MeMgBr to **S5** (Table 5, entry 11).

Table 6 ACA of Various Grignard Reagents RMgBr to Enals **S8** and **S9**



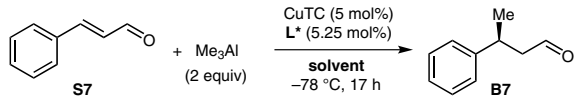
Entry	Enal	R	Adduct	Conv. (%)[a]	Ratio 1,4/1,2	*ee* (%)[b]
1	**S8**	*i*-Bu	*ent*-**A3**	100	36:64	80
2	**S8**	*i*-Pr	*ent*-**A4**	100	67:33	74
3	**S8**	Cy	*ent*-**A5**	100	53:47	86
4	**S8**	$(CH_2)_2Ph$	*ent*-**A6**	100 (50)[c]	67:33	88
5	**S8**	Ph	*ent*-**A7**	88	33:67	80
6	**S9**	*n*-Bu	*ent*-**B2**	100	36:74	88
7	**S9**	*i*-Pr	*ent*-**B4**	100	63:37	65
8	**S9**	Cy	*ent*-**B5**	100 (60)[c]	71:29	89
9	**S9**	$(CH_2)_2Ph$	*ent*-**B6**	100	45:55	74
10	**S9**	Ph	*ent*-**B7**	96	26:74	48

[a] Conversion (conv.) was determined by ^{1}H NMR spectroscopy.
[b] The *ee* was determined by chiral GC.
[c] Isolated yield given in parentheses.

Asymmetric Cu-Catalyzed Conjugate Addition of Me_3Al to Enals

To explore the limits of the methodology, we decided to study again the addition of triorganoaluminum. Previously, we reported that AlR_3 gave 1,2-adducts and aldol products in substantial amounts.[13] At that time, we did not manage to get any 1,4-adduct. To overcome this failure, the reaction was studied again on cinnamaldehyde (**S7**) by using standard conditions for the addition of Me_3Al.[12] A promising result was observed with (*R*)-BINAP (**L1**) as ligand and CuTC as catalyst in THF at –78 °C (Table 7, entry 1). The reaction gave 1,4-adduct **B7** in 66% *ee*, along with 1,2 and aldol products. (*R*)-SYNPHOS (**L6**) and (*R*)-SEGPHOS (**L11**) were then considered. The latter gave **B7** with incomplete conversion, excellent 96% *ee* and improved 1,4/1,2 ratio of 77:23 (entry 3). With this ligand, no traces of the aldol product were observed. Therefore, Me_3Al appeared more efficient than Me_2Zn or MeMgBr for the conjugate addition on cinnamaldehyde (96% *ee* against 62%). Next, several solvents were studied with the aim of enhancing the 1,4-regioselectivity while maintaining the excellent enantiomeric excess. In all cases, the *ee* remained attractive even if it dropped slightly (entries 4–7). TMSCl was also tested as an additive, in the hope that it would be as beneficial as before. Conversion was better, but the 1,4-regioselectivity slightly decreased to 66% and the *ee* fell to 8% (entry 8). Unlike the addition of Grignard reagents, TMSCl was deleterious to the addition of Me_3Al. Finally, the conversion was not improved by using five equivalents of Me_3Al (entry 9).

Table 7 Evaluation of the ACA of Trimethylaluminum on Cinnamaldehyde (**S7**)

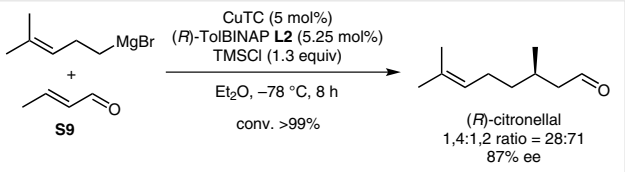


Entry	Ligand L*	Solvent	Conv. (%)[a]	Ratio 1,4/1,2/aldol[a]	*ee* (%)[b]
1	**L1**	THF	83	65:19:16	66
2	**L6**	THF	56	64:36:0	87
3	**L11**	THF	66	77:23:0	96
4	**L11**	EtOAc	51	28:72:0	84
5	**L11**	dioxane	32	39:61:0	85
6	**L11**	THF/dioxane[c]	34	38:62:0	90
7	**L11**	THF/EtOAc[c]	65	47:53:0	93
8[d]	**L11**	THF	83	66:34:0	8
9[e]	**L11**	THF	63	60:0:40	91

[a] Conversion (conv.) was determined by ^1H NMR spectroscopy.
[b] The *ee* was determined by chiral GC.
[c] Solvent ratio 9:1.
[d] Reaction done in the presence of TMSCl (1.3 equiv).
[e] Reaction done with Me_3Al (5 equiv).

Applications of the Asymmetric Cu-Catalyzed Conjugate Addition to Enals

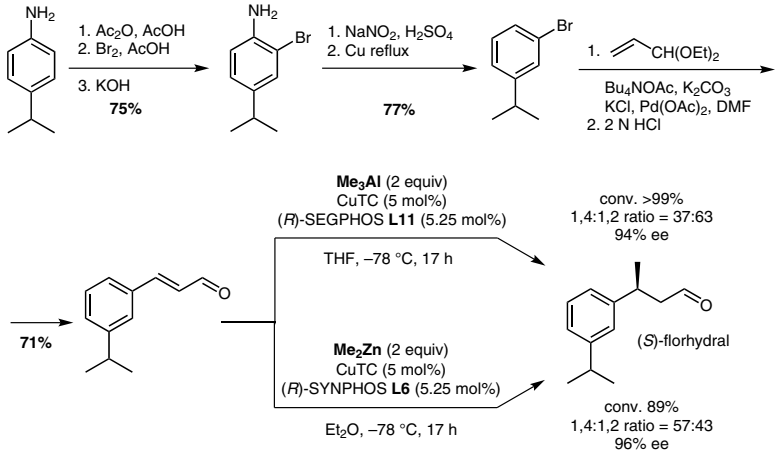
(*R*)-Citronellal was first synthesized by distillation of geraniol in the presence of copper by Treibs,[20] with the process further improved by Kapabas and Kogami.[21] In 1983, Mangeney et al.[22] reported its preparation by conjugate addition of organocuprates on chiral oxazolidines with 85% *ee*. Other method consisted of the asymmetric catalytic isomerization of *N*,*N*′-diethylgeranylamine[23] or geraniol,[24] giving rise to (*R*)-citronellal in 98% and 82% *ee*, respectively. As no other conjugate addition has been tried since 1983, we decided to evaluate the potential of our methodology for the preparation of this natural compound. The asymmetric conjugate addition of a Grignard reagent to **S9** was elected for this purpose (Scheme 4). Applying the conditions previously developed on **S9** gave the desired (*R*)-citronellal in 87% *ee* and a 1,4/1,2 ratio of 28:71. Satisfactorily, the *ee* obtained is in the range of the reported ones. However, the 1,4-regioselectivity dropped significantly compared to previous results. This may be the result of the dilution of the reaction medium due to the lower concentration of the prepared Grignard reagent (1 M) compared to commercially available solutions (usually 3 M).



Scheme 4 Synthesis of (*R*)-citronellal by ACA to **S9**

We were also interested in (*S*)-florhydral, an olfactory compound discovered in 1989 by Chalk.[25] The first synthesis was reported by Brenna et al.[26] and was based on enzymatic catalysis. Seven steps were required to access (*S*)-florhydral in a low yield of 3% and excellent 97% *ee*. In 2006, Paganelli[27] reported the hydroformylation of 3-isoprenylbenzene derivatives to get the compound but with an extremely low *ee* of 5%. Two years later, Stadler[28] described a new pathway based on an asymmetric organocatalytic hydrogenation that provided (*S*)-florhydral in 98% *ee* and 39% yield. We also reported a total synthesis[13] of this natural compound in eight steps with an excellent 99.5% *ee*. The key step was the asymmetric copper-catalyzed conjugate addition of Me_3Al to a β,γ-unsaturated α-keto ester. However, we thought that (*S*)-florhydral could also be obtained by conjugate addition to the appropriate α,β-unsaturated aldehyde. Therefore, we envisioned applying one of the previously developed methodologies to access (*S*)-florhydral more quickly (Scheme 5).

The synthesis began with the preparation of 1-bromo-3-isopropylbenzene. This was done in two steps according to a procedure described by Voskoboynikov,[29] starting from



Scheme 5 Synthesis of (*S*)-florhydral by ACA

p-isopropylaniline. A Heck reaction followed by hydrolysis was then carried out under classic conditions, using acrolein diethyl acetal, affording the desired α,β-unsaturated aldehyde in 71% yield. The enal was first engaged in conjugate addition with Me_3Al. By applying the developed conditions, (*S*)-florhydral was obtained in a very good 94% *ee* but a low 1,4-regioselectivity. The conjugate addition of Me_2Zn appeared better, as it provided the desired compound in 96% *ee* and better 1,4-regioselectivity (57% against 37%) (Scheme 5).

We have reported herein our complete studies on the asymmetric copper-catalyzed conjugate addition of organometallic reagents to α,β-unsaturated aldehydes. Three sets of conditions were successfully developed. The first one consisted of the addition of organozinc reagents. The use of (*R*)-H_8BINAP as ligand and CuTC as catalyst provided 1,4-adducts in good to excellent *ee*'s (up to 95%) and moderate to excellent 1,4/1,2 ratios (up to 100:0). The second one concerned the addition of Grignard reagents in the presence of (*R*)-TolBINAP as ligand and TMSCl as additive. Under these conditions, several enals successfully gave rise to β-substituted aldehydes in *ee*'s up to 90%. However, the regioselectivity remained moderate to good. In a last set of experiments, we developed the conjugate addition of trimethylaluminum. Here, the ligand of choice was (*R*)-SEGPHOS, which allowed the formation of the desired 1,4-adduct in excellent 96% *ee* and a good 1,4/1,2 ratio of 77:23. Finally, we applied our methodologies to the synthesis of natural compounds. We were able to access (*R*)-citronellal as well as (*S*)-florhydral in a few steps with very good *ee*'s (87% and 96% respectively).

All reagents were purchased from Sigma-Aldrich and Acros or FrontierScientific and were used as received. Solvents were dried by filtration over alumina previously activated at 350 °C for 12 h under N_2 before use. Grignard reagents were synthesized in Et_2O by addition of the corresponding bromide to magnesium or were commercially available (EtMgBr, MeMgBr, and PhMgBr; 3 M in Et_2O); commercially available Me_2Zn (1.2 M in toluene), Et_2Zn (1 M in hexane), and Me_3Al (2 M in heptane) were also used. Phosphoramidite ligand studies as well as GC chromatograms are reported in the Supporting Information. All compounds in this paper have already been reported in the literature (see Supporting Information).

ACA with Dialkylzinc Reagents; General Procedure

A solution of CuTC (5 mol%) and (*R*)-H_8BINAP (**L3**; 5.25 mol%) in Et_2O (1 mL) was stirred for 20 min at r.t., followed by 20 min at 0 °C or –20 °C. R_2Zn (2 equiv) was then added, and after 15 min, a solution of the enal (0.25 mmol) in Et_2O (0.5 mL) was slowly added over 1 h. The reaction mixture was stirred at 0 °C or –20 °C for 6–17 h before being quenched by 1 M aq HCl. The aqueous phase was extracted by Et_2O (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude α,β-unsaturated aldehydes. The products were isolated either directly by chromatography (silica gel, pentane–Et_2O) or after reduction to the corresponding alcohol (using $NaBH_4$ in a THF–MeOH mixture).

ACA with Grignard Reagents; General Procedure

A solution of CuTC (5 mol%) and (*R*)-TolBINAP (**L2**; 5.25 mol%) in Et_2O (1 mL) was stirred for 20 min at r.t., followed by 20 min at –78 °C. RMgBr (2 equiv) was then added, and after 15 min, a solution of the enal (0.25 mmol) and TMSCl (1.3 equiv) in Et_2O (0.5 mL) was slowly added over 1 h. The reaction mixture was stirred at –78 °C for 8 h before being quenched by 1 M aq HCl–MeOH. The aqueous phase was extracted by Et_2O (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude α,β-unsaturated aldehydes. The products were isolated either directly by chromatography (silica gel, pentane–Et_2O) or after reduction to the corresponding alcohol (using $NaBH_4$ in a mixture of THF and MeOH).

ACA with Me_3Al; General Procedure

A solution of CuTC (5 mol%) and (*R*)-SEGPHOS (**L11**; 5.25 mol%) in THF (1 mL) was stirred for 20 min at r.t., followed by 20 min at –78 °C. Me_3Al (2 equiv) was then added, and after 30 min, a solution of cinnamaldehyde (**S7**; 0.25 mmol) in THF (0.5 mL) was slowly added over 1 h. The reaction mixture was stirred at –78 °C for 17 h before being

quenched by 1 M aq HCl. The aqueous phase was extracted by Et_2O (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give β-methyl-substituted aldehyde **B7**.

Acknowledgment

We thank the Swiss National Research Foundation (grant N° 200020-126663) and COST action D40 (SER contract N° C07.0097) for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562487.

References

(1) (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (b) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796. (c) Harutyunyan, S. R.; Den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. *Chem. Rev.* **2008**, *108*, 2824.
(2) (a) Bräse, S.; Höfener, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 7879. (b) Ay, S.; Nieger, M.; Bräse, S. *Chem. Eur. J.* **2008**, *14*, 11539. (c) For a racemic example without copper, see: Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471.
(3) Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5505.
(4) Ibrahem, I.; Santoro, S.; Himo, F.; Còrdova, A. *Adv. Synth. Catal.* **2011**, *353*, 245.
(5) As a reference for Rh-catalyzed ACA to enals, see: (a) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000. (b) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (c) Tokunaga, N.; Hayashi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 607.
(6) As a reference for Pd-catalyzed ACA to enals, see: Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **2004**, 1822.
(7) Hird, A. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1276.
(8) Des Mazery, R.; Pullez, M.; Lòpez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966.
(9) Garcìa, J. M.; Gonzàlez, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C. *Chem. Eur. J.* **2008**, *14*, 8768.
(10) Fañanas-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2010**, *132*, 13152.
(11) Mao, B.; Fañanas-Mastral, M.; Feringa, B. L. *Org. Lett.* **2013**, *15*, 286.
(12) Gremaud, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 794.
(13) Palais, L.; Babel, L.; Quintard, A.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1988.
(14) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.
(15) Phosphoramidites were also envisioned as ligands in these studies (see ref. 12) but appeared less attractive, as they are not commercially available. Nevertheless, results are presented in the Supporting Information.
(16) Knopf, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835.
(17) Vuagnoux-d'Augustin, M.; Alexakis, A. *Tetrahedron Lett.* **2007**, *48*, 7408.
(18) Chuit, C.; Foulon, J.-P.; Normant, J. F. *Tetrahedron* **1980**, *36*, 2305.
(19) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (d) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.
(20) Treibs, W.; Schmidt, H. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 2335.
(21) (a) Kapabas, B. H. US Patent 118498, **1958**. (b) Kogami, K.; Kumanota, J. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2508.
(22) (a) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1983**, *24*, 373. (b) Mangeney, P.; Alexakis, A.; Normant, J. *Tetrahedron* **1984**, *40*, 1803.
(23) Akutagawa, S. In *Comprehensive Asymmetric Catalysis*; Vol. 3; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**, Chap. 41.4.
(24) (a) Mantilli, L.; Gerard, D.; Torche, S.; Besnard, C.; Mazet, C. *Chem. Eur. J.* **2010**, *16*, 12736. (b) Mantilli, L.; Mazet, C. *Chem. Commun.* **2010**, *46*, 445.
(25) Chalk, A. J. EP 0368156, **1989**.
(26) Abate, A.; Brenna, E.; Negri, C. D.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry* **2002**, *13*, 899.
(27) Paganelli, S.; Ciappa, A.; Marchetti, M.; Scrivanti, A.; Matteoli, U. *J. Mol. Catal. A* **2006**, *247*, 138.
(28) Stadler, M.; List, B. *Synlett* **2008**, 597.
(29) Izmer, V. V.; Lebedev, A. Y.; Nikulin, M. V.; Ryabov, A. N.; Asachenko, A. F.; Lygin, A. V.; Sorokin, D. A.; Voskoboynikov, A. Z. *Organometallics* **2006**, *25*, 1217.