ChemPubSoc Europe

DOI: 10.1002/chem.201500292

CHEMISTRY
A European Journal
Full Paper

Asymmetric Addition

Formation of Contiguous Quaternary and Tertiary Stereocenters by Sequential Asymmetric Conjugate Addition of Grignard Reagents to 2-Substituted Enones and Mg–Enolate Trapping

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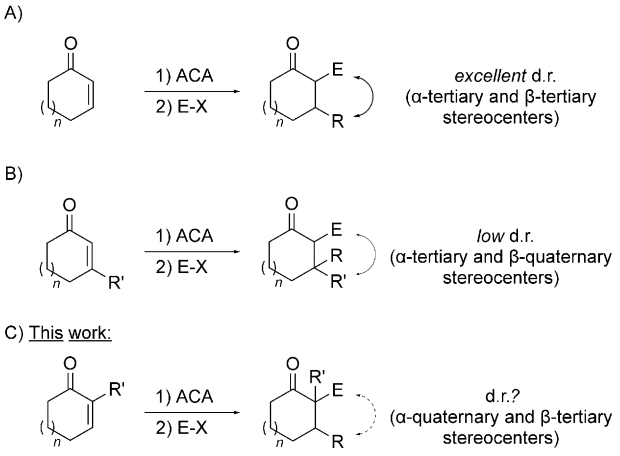
Abstract: Herein a comprehensive study is provided on the asymmetric conjugate addition (ACA) of Grignard reagents to α-substituted cyclic enones. After the elucidation of the optimal experimental conditions, the scope of Grignard reagents and Michael acceptors was examined. Whereas secondary Grignards gave better enantioselectivities with 2-cyclopentenones, both linear and branched Grignard reagents were tolerated for the ACA to 2-methylcyclohexenone. The sequential ACA–enolate trapping, which leads to quaternary stereocenters, was then studied. Thus, many electrophiles have been tested, thereby giving rise to highly functionalized cyclic ketones with contiguous α-quaternary and β-tertiary centers. The present technique is believed to bring a new approach to versatile terpenoid-like skeletons of bioactive natural products. Straightforward derivatizations of enantioenriched saturated cyclic ketones further support the potential of the present methodology in synthesis.

Introduction

One-pot synthesis of multiple stereogenic centers is a tremendously desirable process in organic chemistry.[1] Indeed, stereo- and regiocontrolled cascade reactions can be powerful methods to install complex molecular scaffolds such as natural products precursors. However, sequential one-pot transformations are not always compatible with all chemical events, especially when organometallic complexes are involved. Nevertheless, transition-metal-catalyzed conjugate addition of organometallic reagents is indeed compatible with tandem and/or sequential reactions. Sequential conjugate addition followed by metal–enolate trapping has been described for various metal-enolates and electrophiles.[2] This transformation has been studied for the formation of contiguous tertiary stereocenters (Scheme 1A). Owing to the emergence of the asymmetric conjugate addition (ACA) to trisubstituted enones, the trapping of the consecutive metal–enolates emerged soon after (Scheme 1B). Unfortunately, quaternary centers poorly discriminate between the enolate faces, thus leading to a low level of diastereoselection. The case of α-substituted cyclic enones offers a promising third route for the sequential ACA–enolate trapping. Indeed, it allows for the construction of contiguous quaternary and tertiary centers (Scheme 1C). The prevalence of quaternary centers in nature in conjunction with the need for techniques based on cheap and readily available chemicals convinced us to focus on the development of the ACA–enolate trapping sequence.[3,4] Preliminary results suggested that the β substituent efficiently shields one face of the enolate, thus leading to high diastereomeric ratios (d.r.).[5]



Scheme 1. Sequential ACA-enolate trapping.

The ACA to α-substituted cyclic enones has already been considered in our laboratory.[6] A catalytic system was optimized in 2007, and it was found that the complex Cu/phosphoramide $\mathbf{L_1}$ was an active catalyst for the ACA to 2-methylcyclohexenone too. However, even after optimizations, the challenge of ACA to 2-methylcyclopentenone **4** and **5** remained.[6c] Furthermore, a sequential ACA–enolate trapping event based on these prior results was developed by Cramer and co-workers.[7] We thus decided to face three challenges at the same time: ACA to α-substituted cyclic enones, the development of this methodology to five-membered rings, and the

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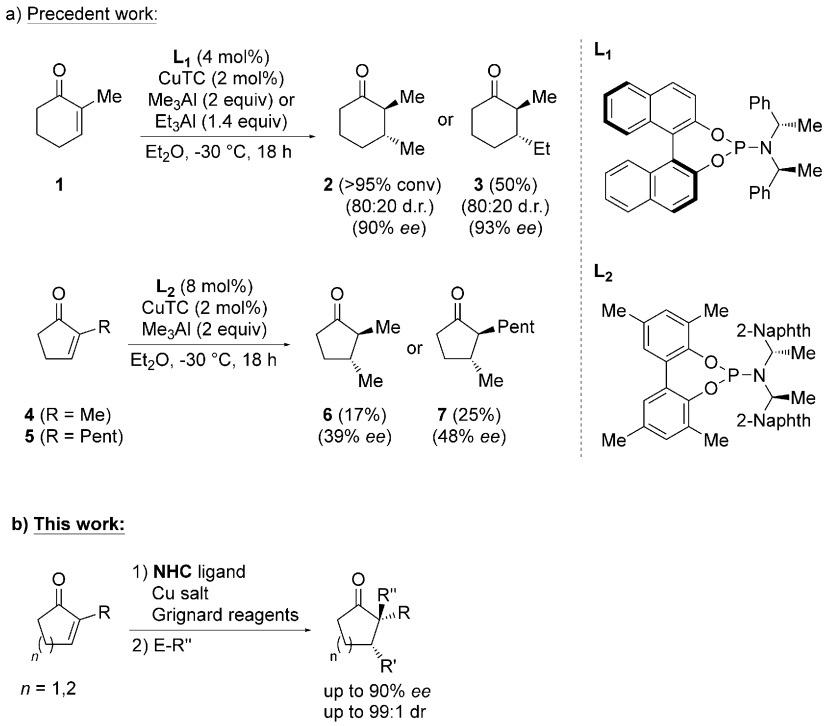
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500292.



Scheme 2. ACA to α-substituted enones.

optimization of a tandem ACA–enolate trapping for a broad scope of electrophiles (Scheme 2).

In this article, the scope of the ACA of Grignard reagents to α-substituted cyclic enones will be overviewed. After all the optimization experiments, the scope of Grignard reagents and Michael acceptors will be shown. The sequential ACA–enolate trapping will then be detailed through a comprehensive survey of electrophiles, and a few derivatizations will eventually demonstrate the synthetic potential of our method towards natural product synthesis.[5]

Results and Discussion

ACA to α-substituted enones

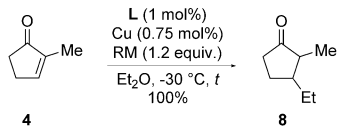
The ACA to 2-methylcyclohexenone **4** was first studied with classical ACA catalysts. The previous results were reproduced using $\mathbf{L_2}$, as well as with other phosphoramidites, phosphinamines, and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP).[6c] In addition to the disappointingly low enantiomeric excess (*ee*) values observed, this method is essentially limited by itself. Indeed, organoaluminum reagents are mostly useful for the introduction of a methyl moiety. Also, trimethylaluminum is a relatively cheap reagent. Numerous research groups have successfully demonstrated the versatility of trimethylaluminum in ACA throughout highly selective processes. However, the number of organoaluminum derivatives readily available is rather limited, so we focused on Grignard reagents instead. In addition, it was predicted that the reactivity of the resulting Mg–enolate would be higher than Zn– or Al–enolates. No improvement was observed when a phosphoramidite or phosphinamine or BINAP ligand was used in combination with copper thiophene carboxylate (CuTC) for the ACA of ethylmagnesium bromide to **4**. It was then decided to study the influence of N-heterocyclic carbene (NHC) ligands for this transformation. The ACA of EtMgBr carried out with carbene ligands $\mathbf{L_3}$ and C_2-symmetric $\mathbf{L_4}$ furnished a racemic mixture of the desired saturated ketone **8** (Table 1, entries 1 and 2). The same results were obtained with $\mathbf{L_5}$ (Table 1, entry 3). The breakthrough came with Mauduit-type NHC $\mathbf{L_6}$[8] for the addition of EtMgBr in the presence of copper triflate: full conversion and a promising 43% *ee* was obtained (Table 1, entry 4). When diethylzinc was tested under the same conditions, no reactivity was observed. Neither $\mathbf{L_7}$ (Table 1, entry 5, 16% *ee*) nor $\mathbf{L_8}$ (Table 1, entry 6, *rac*) showed satisfying results. A complex mixture of compounds was detected with TaniaPhos-type ligand $\mathbf{L^8}$ (Table 1, entry 7), thus narrowing the path towards an extensive screening of ferrocene-based ligands.[9]

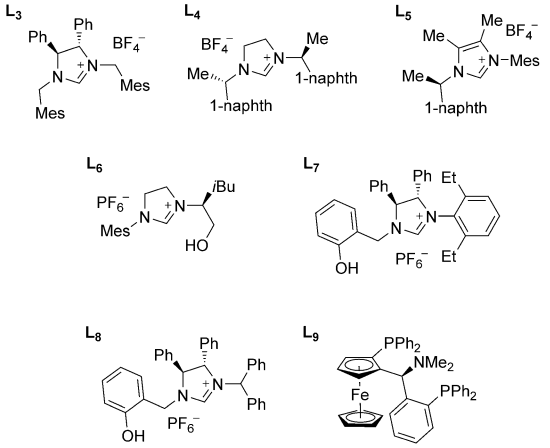
It should be noted that adduct **8** was obtained as *cis*/*trans* mixture in variable amounts. As the enantioselectivity is determined during the conjugate addition step, both diastereomers have the same *ee*. This was checked in many instances. Isomerization with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided mixtures that contained >90% of the *trans* isomer.

Various solvents were surveyed for the ACA of EtMgBr to 2-methylcyclopentenone **4** in the presence of a catalytic amount of $Cu(OTf)_2/\mathbf{L_6}$ complex (formed in situ, Table 2). Acyclic ethers gave significantly higher results than the cyclic ones (Table 2, entries 1–3 versus entries 8 and 9). Although diethyl ether was the best choice for this transformation, the use of diisopropyl ether was not detrimental, and **8** was obtained in 37% *ee* (Table 2, entry 2). Comparable results were obtained with cyclopentyl methyl ether (Table 2, entry 3, 26% *ee*), toluene (Table 2, entry 4, 25% *ee*), and dichloromethane (Table 2, entry 5, 21% *ee*), probably indicating that the nature of the solvent (e.g., polarity, coordination abilities) is not a determining factor for the species involved in the enantio-determining step. Moderate results were obtained with 2-methyltetrahydrofuran (Table 2, entry 7, 14% *ee*) and methyl *tert*-butyl ether (Table 2, entry 8, 13% *ee*). A racemic mixture was recovered with tetrahydrofuran and dimethoxyethane (Table 2, entries 9 and 10).

With the best solvent in hand, and with $\mathbf{L_6}$ as reference, an extensive screening of various NHCs, including Mauduit-type

Table 1. Screened catalytic systems for the ACA to 2-methylcyclopentenone.

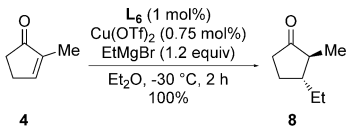




Entry	Ligand	Copper salt	R_nM	*ee* [%][a]
1	L_3	CuTC	EtMgBr	–[b]
2	L_4	$Cu(OTf)_2$	EtMgBr	–[b]
3	L_5	CuTC	EtMgBr	–[b]
4	L_6	$Cu(OTf)_2$	EtMgBr	43
5	L_7	$Cu(OTf)_2$	EtMgBr	16
6	L_8	$Cu(OTf)_2$	EtMgBr	–[b]
7	L_9	$Cu(OTf)_2$	EtMgBr	[c]

[a] Determined by chiral GC. [b] A mixture of racemic 3-ethyl-2-methylcyclohexanone, 3-ethyl-1-methyl-cyclohex-1,2-diene, and 1-ethyl-3-methylcyclohex-2-en-1-ol was recovered. [c] Not determined.

Table 2. Solvent optimization for the ACA of ethylmagnesium bromide to 2-methylcyclopentenone.



Entry[a]	Solvent	*ee* [%][b]
1	Et_2O	43
2	iPr_2O	37
3	CPME[c]	26
4	toluene	25
5	CH_2Cl_2	21
6	2-MeTHF	14
7	MTBE[c]	13
8	dioxane	*rac*
9	THF	*rac*
10	DME[c]	*rac*

[a] The reactions were all stopped after total consumption of the starting material. [b] Determined by chiral GC. [c] CPME = cyclopentyl methyl ether; MTBE = methyl *tert*-butyl ether.

NHCs, was achieved for the ACA of ethylmagnesium bromide to α-methylcyclopentenone (Figure 1). We first examined the influence of a chiral backbone (L_{10}), but a racemic mixture of the desired saturated ketone **8** was detected.

Non-natural amino acid based NHCs such as L_{10} and L_{11} were also unsuccessful. Compound L_{12} was synthesized from (1*R*,2*R*)-2-amino-1,2-diphenylethanol, but no enantioselectivity was measured with **8**. The first Mauduit-type NHCs tested were L_{13} and L_{14}, but only poor *ee* values were observed. Various scaffolds were then tried, although modest *ee* values or racemic mixtures were obtained (L_{15}–L_{21}). As expected, the ACA of EtMgBr to 2-methylcyclohexenone catalyzed by complex Cu/*ent*-L_6 gave *ent*-**8** with −41% *ee*. The influence of the blocking part of the chelating arm was further optimized. The relative effect of the mesitylamine (*ent*-L_6, −41% *ee*) and the mesitylmethanamine (L_{22} and L_{23}, 22% and 15% *ee*, respectively) group negatively affected the enantioinduction. It was eventually found that bulkier aromatic groups considerably increased the *ee* values measured for 3-ethyl-2-methylcyclopentanone. This study ended with the test of L_{27} (60% *ee*), which remained as our best ligand for the next experiments. The corresponding ligand that bore a pendant isobutyl group—that is, leucinol-based

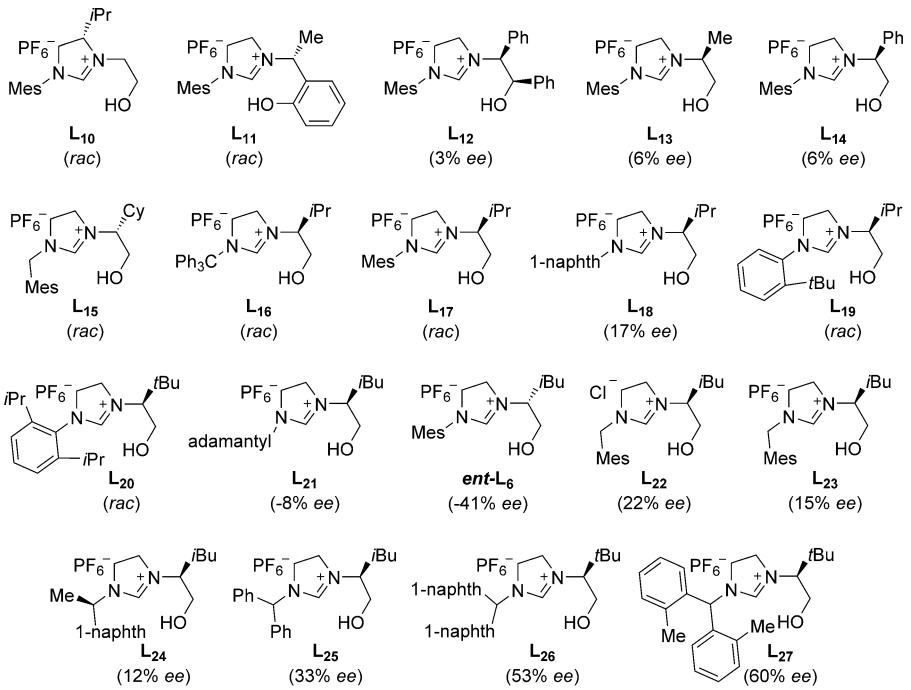


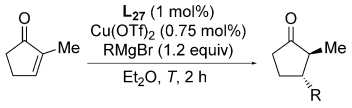
Figure 1. NHC ligands surveyed for the ACA of ethylmagnesium bromide to 2-methylcyclopentenone.

NHC—led to lower *ee* values (42%, not shown). Although this study highlighted the inefficiency of valine-based Mauduit-type NHCs as well as other natural amino acid based NHCs, nowadays *tert*-leucinol can also be considered to be a relatively cheap starting material for this methodology. Further studies of catalyst recycling might support this hypothesis and encourage prospective large-scale processes.

The influence of temperature on the reaction outcome was also studied. Optimal results were found for temperatures that ranged from −20 to −40 °C. Slightly higher yields and regioselectivity were obtained at −30 °C.

The scope of Grignard reagents was then examined for the β-alkylation of α-methylcyclopentenone. No stereocontrol was obtained for the transfer of the methyl moiety using MeMgBr. Concerning linear Grignard reagents (Table 3, entries 2–6), the

Table 3. Scope of Grignard reagents.



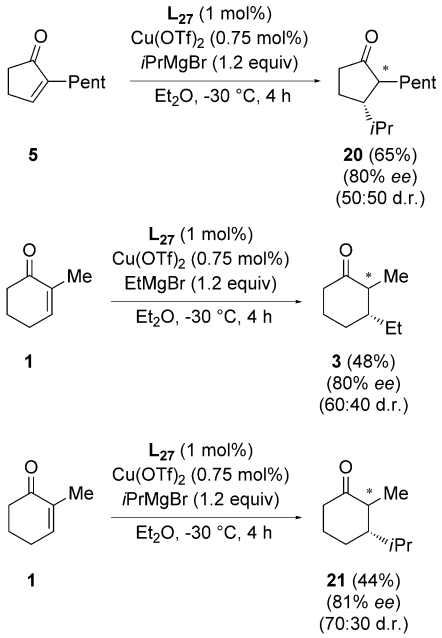
4 6-19

Entry[a]	Product	RMgBr	Conv. [%]	d.r.[b]	*ee* [%][b]
1	**6**	Me	–[c]	50:50	–
2	**8**	Et	75	82:18	60
3	**9**	*n*Pr	65	93:7	52
4	**10**	*n*Bu	90	82:18	48
5	**11**	butenyl	91	94:6	24
6	**12**	phenethyl	–[c]	94:6	34
7	**13**	*i*Bu	88	87:13	24
8[d]	**14**	*i*Pr	89	60:40	90
9	**15**	3-pentyl	71	82:18	71
10	**16**	5-heptyl	60	70:30	74
11	**17**	*c*Pent	85	52:48	83
12	**18**	*c*Hex	91	60:40	80
13	**19**	*c*Hept	65	52:48	83

[a] The reactions were carried out in dry diethyl ether at −30 °C with 1 mol% of L_{27}, 0.75 mol% of copper triflate, and 1.2 equiv of Grignard reagent. [b] Determined by gas chromatography. The absolute configuration was determined in our preliminary communication.[5] [c] A mixture of starting material, desired product, and 1,2-addition products. [d] 2 mol% of L_{27} and 1.67 mol% of copper triflate.

enantiomeric excesses did not exceed 60% *ee* despite excellent chemicals yields and good d.r. (>82:18). The reaction proceeded smoothly to afford the desired 1,4-adducts so that the crude material was simply purified by a path of silica gel to separate the product from the catalyst. Branched Grignard reagents led to much more interesting results. Indeed, for five-membered rings, the introduction of an isopropyl moiety to a cyclopentane motif is of critical importance in natural product synthesis of terpinoids. To our delight, *i*PrMgBr was treated with 2-methylcyclopentenone in the presence of copper to give the targeted saturated ketone in 90% *ee* and 89% isolated yield. Having access to this improved result required an elevated amount of catalyst loading (2 mol% in copper triflate instead of 0.75) and a 4 M solution of *i*PrMgBr in diethyl ether (compared to 3 M previously). The concentration of the reaction media was also tested but was not significant; the quality of the Grignard reagent rather than the overall dilution of the system led to enhanced results. Additional tests were conducted with 3-pentyl- and 5-heptylmagnesium bromides, thus leading to the corresponding ketones in 71 and 74% *ee*. ACA of cyclic Grignard reagents allowed for the preparation of ketones **17**–**19** in 80 to 83% *ee* and high yields.

The methodology was extended to various cyclic enones (Scheme 3). When α-pentylcyclopentenone **5** was tested under



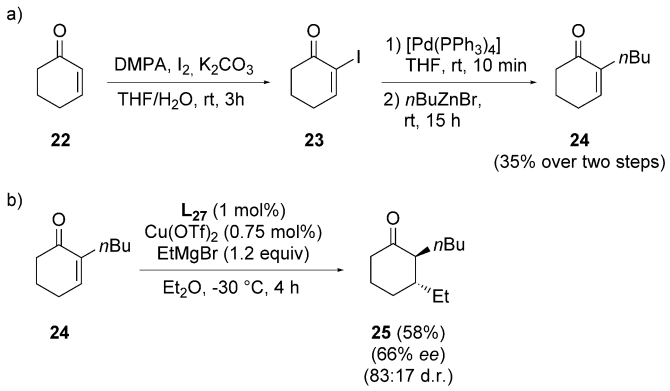
Scheme 3. ACA to α-substituted enones: Scope of substrates.

our optimized conditions, an interesting 80% *ee* was obtained. Comparable results were observed for the ACA of ethyl- and isopropylmagnesium bromide to six-membered rings (80 and 81% *ee*, respectively). It is worth noting that the addition of both linear and branched moieties was tolerated when applying our strategy to 2-methylcyclohexenone.

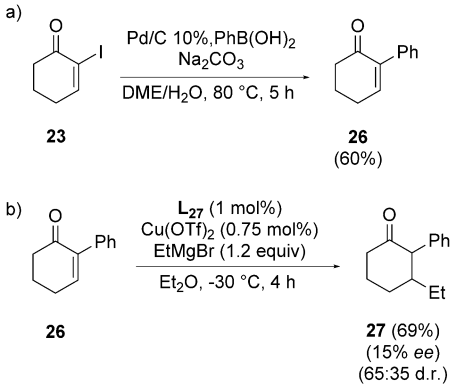
Analogously to five-membered rings, we next wanted to study the effect of an α-alkyl chain for cyclohexenones (Scheme 4). The synthesis of **24** was achieved after α-iodination of cyclohexenone followed by a palladium(0)-catalyzed Negishi-type coupling to afford the desired 2-*n*-butylcyclohexenone in 35% yield over two steps.[10] The ACA of EtMgBr to **24** yielded **25** in 58% yield and 66% *ee*.

Following the same strategy, the influence of α-aryl groups has also been evaluated (Scheme 5). Ketone **26** was synthesized from **23** by Suzuki-type coupling in 60%,[11] and ACA of EtMgBr gave a disappointing 15% *ee*. The present methodology is restricted to α-alkyl substituted cyclic enones.

The ACA to α-substituted cyclic enones is a versatile approach to introduce two stereodefined tertiary centers. Whereas the absolute configuration of the β-stereogenic carbon is determined by the Cu/NHC chiral complex, the relative configuration of these carbon atoms—that is, the ratio



Scheme 4. ACA to α-phenylcyclohexenone.



Scheme 5. ACA to α-butylcyclohexenone.

between the *cis* and *trans* diastereomers—is directly correlated to the enolate-trapping event, which can be improved by an equilibration using DBU in methanol. For all the results exposed above, the sequence ends with non-diastereoselective Mg-enolate protonation using a diluted hydrochloric acid solution. Different options to circumvent this problem have drawn our interest. All are based on the simple concept of increasing the steric hindrance of the protic source. Nonchiral stoichiometric carboxylic esters have been tested but no significant improvement was noted.[12] Fehr and co-workers proved that an ephedrine-based reagent allowed for the stereoselective protonation of Li-enolates.[13] The tests carried out with their system did not lead to significantly higher d.r.. We eventually considered using (+)-BINOL and (−)-BINOL (BINOL = 1,1′-bi-2-naphthol) with a potential match/mismatch effect, but these experiments were not conclusive. The solution to introduce larger electrophiles that also react at lower temperature was the most successful approach.

Sequential ACA-enolate trapping

Our interest in developing the ACA of Grignard reagents to α-cyclopentenone lies in the possibility of using the resulting Mg–enolate. The sequential conjugate addition of lithium cuprate reagents followed by enolate trapping is well described in the literature and has formed the scaffold of many total syntheses of bioactive compounds.[2] Whereas the reactivity of Zn– and Al–enolates is relatively low, Mg-enolates are the next best after Li–enolates. Owing to our interest in natural products and our experimental results, the sequential ACA of Grignard reagents and Mg–enolate trapping starting from 2-substituted cyclic enones was extended. This technique would give access to contiguous quaternary and tertiary stereodefined carbon atoms.

To achieve this sequence, many challenges must be overcome: i) Tetrasubstituted metal-enolates might be too sterically congested and thus annihilate the trapping event. ii) Typically, sequential conjugate additions and enolate trapping might require a large quantity of electrophile together with a cosolvent (THF, hexamethylphosphoramide, and so forth). iii) Additional transition metals are sometimes needed, most notably for allylations.

Alkylations

We first investigated the behavior of Mg–enolates in the presence of benzyl bromides (Figure 2). To our delight, an excellent level of diastereoselection was measured for all the examples

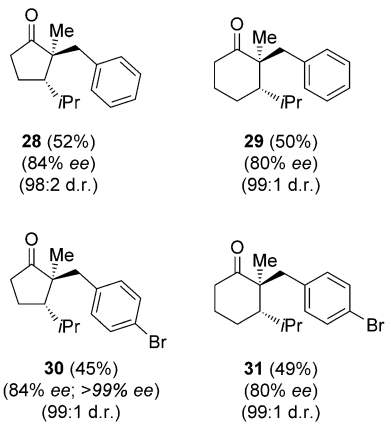
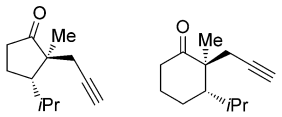


Figure 2. Benzylation of Mg–enolates.

(98:2 to 99:1 d.r.), and ketones **28**–**31** were isolated in practical yields. As expected, the electrophile approached from the upper face of the enolate, that is, the isopropyl and the benzyl groups are in a *trans* relationship. This, as well as the absolute configuration, was previously confirmed by X-ray analysis of **30**.[5]

We next aimed to provide more data on the trapping of tetrasubstituted enolate using propargyl halides (Figure 3). This has been previously discussed by Cramer and co-workers with Al-enolates,[7] even though rather large amounts of reagents and reactant were required and the reaction was limited to less-accessible propargyl iodides. In our example, only two equivalents of commercially available propargyl bromide were enough to deliver the desired compounds in high d.r. (up to 99:1).

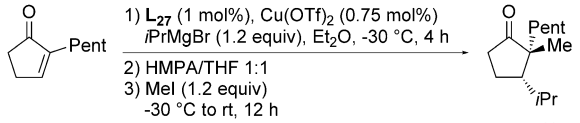


32 (85%)
(84% *ee*)
(99:1 d.r.)

33 (40%)
(80% *ee*)
(99:1 d.r.)

Figure 3. Propargylation of Mg–enolates.

The alkylation of enolates using non-activated electrophiles is particularly challenging. However, their application to the synthesis of biologically active substances such as pheromones led us to investigate this particular case.[14] We thus took advantage of the flexibility of our method to carry out an ACA to α-pentylcyclopentenone followed by Mg–enolate trapping using methyl iodide in 64% overall yield (Scheme 6). Indeed,



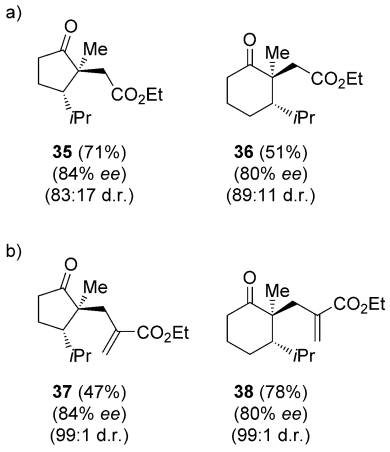
5

34 (64%)
(84% *ee*)
(87:13 d.r.)

Scheme 6. Formation of trialkylated cyclopentanone.

other aliphatic iodides did not furnish the desired compounds. Although a slightly lower d.r. of 87:13 was recovered, the sequence gives rise to a unique trialkylated cyclopentanone **34**.

The installation of easily derivatizable functions is of the utmost importance when developing new methodologies (Figure 4). We thus decided to test a simple alkylation of tetrasubstituted Mg–enolates using ethyl iodoacetate under the conditions shown in Scheme 6. Slightly lower d.r. values than the aforementioned results were measured (83:17 and 89:11), but the synthesis of **37** and **38** (99:1 d.r.) afforded highly satisfying results.[15]



35 (71%)
(84% *ee*)
(83:17 d.r.)

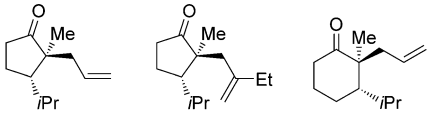
36 (51%)
(80% *ee*)
(89:11 d.r.)

37 (47%)
(84% *ee*)
(99:1 d.r.)

38 (78%)
(80% *ee*)
(99:1 d.r.)

Figure 4. Trapping of Mg–enolates with an activated electrophilic alkyl moiety.

Allylation reactions were studied as well. Even though many previous works have studied these reactions, their application in tandem ACA–enolate trapping has often encountered issues. Whereas Zn–enolates can be trapped with allyl halides, a catalytic amount of $[Pd(PPh_3)_4]$ is required for the reaction to proceed.[16] In the case of tetrasubstituted Mg–enolates, the sequence smoothly delivered the expected compounds **39**–**41** in 62–65% isolated yields (Figure 5) without added Pd. In



39 (65%)
(84% *ee*)
(98:2 d.r.)

40 (65%)
(84% *ee*)
(99:1 d.r.)

41 (62%)
(80% *ee*)
(99:1 d.r.)

Figure 5. Allylation of Mg–enolates.

contrast to the previous example described by Piers et al. with Li–enolate (see below for the example with methyl vinyl ketone), the sequence using 3-bromo-2-ethylpropene reached full conversion under Pd-free conditions.[17]

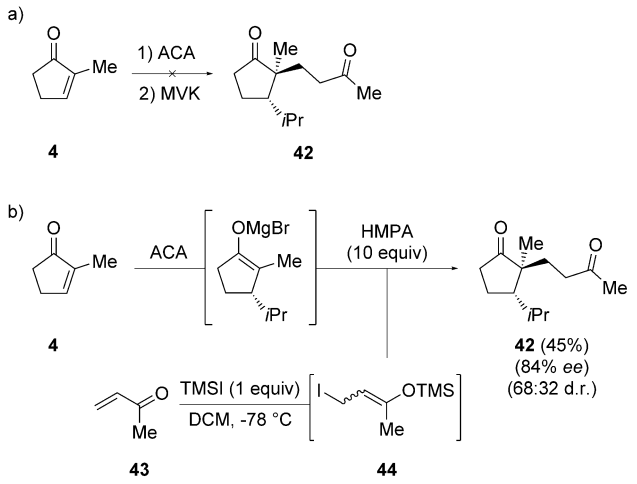
We have already described in our preliminary communication[5] how this methodology can be applied to the formal synthesis of (+)-4,5-deoxyneodolabelline,[18] Crinipellin B,[17] and Guanacastepene A.[19]

Michael additions

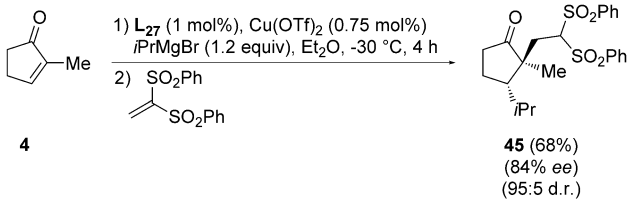
We then carried out the relevant sequential ACA–Michael addition, even if this sequence is certainly among the most challenging. Methyl vinyl ketone (MVK) was examined first, but only oligomers were detected. This is due to the competitive pathways between enolates that lead to an alternative pathway, oligomerization. The problem could be circumvented by choosing allyliodide derivative **45**, which was formed after the reaction of MVK with trimethylsilyliodine in dichloromethane at low temperature.[20] The resulting 1,5-diketone could be isolated in 45% yield after reaction of **44** and the Mg–enolate, which were both formed in situ (Scheme 7). The synthesis of **42** and analogues addresses the need for enantioenriched trisubstituted cyclopentanones in natural products syntheses, notably in bioactive terpenoids. In this particular example, Guanacastepene A was clearly identified as a candidate for the direct application of our methodology.[19]

The reaction between sterically congested tetrasubstituted Mg–enolates and phenyl vinyl disulfone was also attempted.[21] To our delight, functionalized ketone **45** was isolated in 68% yield and 95:5 d.r. (Scheme 8). Thanks to these versatile sulfones, **45** could be derivatized into various targets.[22]

The reaction of Li–enolates with α,β-unsaturated electrophiles was studied by Posner and co-workers. They notably reported on a particular case of enolate trapping, namely, the Michael–Michael ring-closure sequence (MIMIRC).[23] In 1981, the tandem MIMIRC based on two consecutive Michael additions followed by a Wittig-type cyclization was disclosed for



Scheme 7. Mg–enolate trapping with MVK.

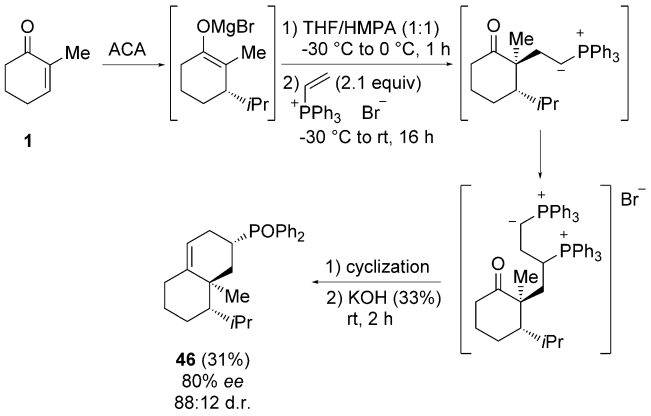


Scheme 8. Michael–Michael addition.

the reaction between Li–enolates and triphenylvinylphosphonium bromide, thereby allowing the formation of cyclopropanes and steroids.[23b] The same principle was applied to our contemporary system (Scheme 9). Inspired by our previous results in sequential ACA–Michael additions,[21] the tetrasubstituted Mg–enolate generated from **1** was trapped with triphenylvinylphosphonium bromide to give a phosphonium ylide, which was again trapped with another equivalent of triphenylvinylphosphonium bromide. The second equivalent of triphenylvinylphosphonium bromide led to the formation of another phosphonium ylide, which reacted with the carbonyl to give the cyclized product **46** in 31% overall yield after four steps.

Halogenation

The halogenation of Mg-enolates was equally successful (Scheme 10). The bromination of Mg–enolates has been already reported using molecular bromine. In our case, we have developed a standard procedure for the halogenation of tetrasubstituted enolates that results from ACA. *N*-Iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), and *N*-chlorosuccinimide (NCS) have been used to allow for the halogenation of Mg–enolates. The halogenation of enolates offers a practical platform for further derivatizations and with, for instance, organometallic reagents or transformation that involves radicals.



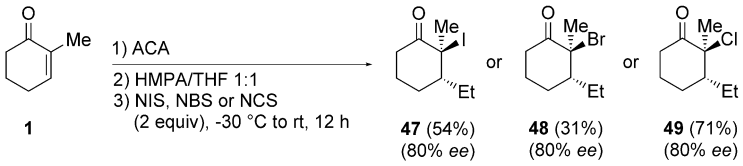
Scheme 9. MIMIRC concept applied to the ACA to α-substituted enones.

Cyanation

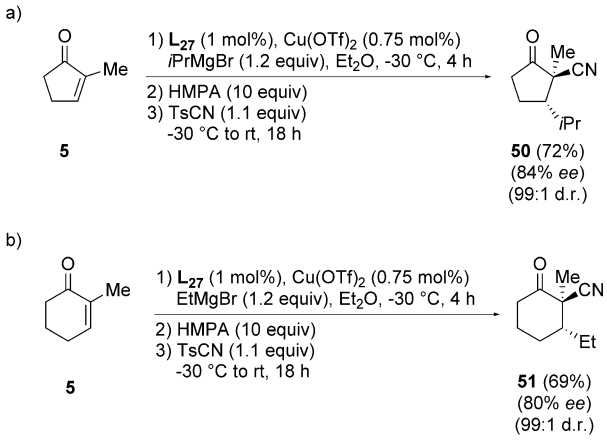
We optimized our strategy to form enantioenriched α-cyanoketones (Scheme 11). The cyanation of Li–enolates is well known; however, to the best of our knowledge, the conjugate addition–cyanation sequence has never been disclosed, not even in the racemic version.[24] To our delight, the sequence was carried out to successfully give ketone **50** and **51** in 72 and 69% yield, respectively. Cyano groups can be derivatized into carboxylic acids or amines, thereby affording numerous synthetic options.

O-trapping

The *O*-trapping of tetrasubstituted enolates has been reported but can often be problematic (low yield, low selectivity).[25] The



Scheme 10. Halogenation of tetrasubstituted Mg–enolates.



Scheme 11. Cyanation of Mg–enolates.

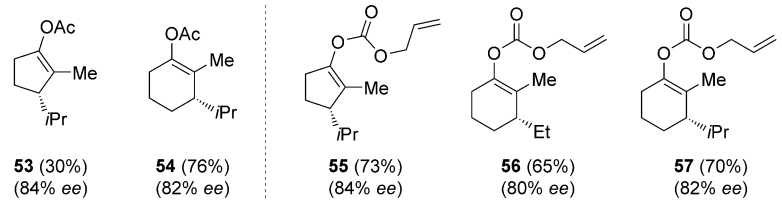


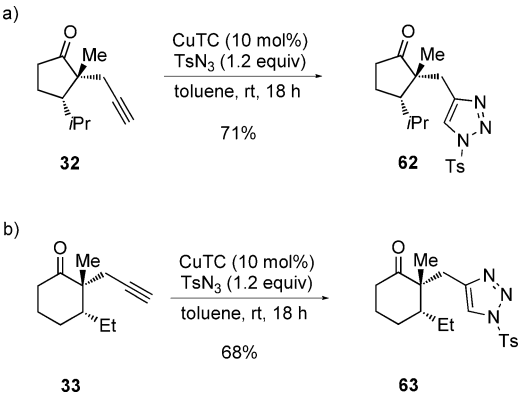
Figure 6. *O*-trapping of enolates.

synthetic potential of this technique led us to consider their reactivity towards acetic anhydrides and allyl chloroformates (Figure 6). Acetates **53** and **54** have been prepared in 30 and 76% yield, respectively. Allyl enol carbonates **55**–**57** could be synthetized in good yields too (65–73%). We have already shown in our preliminary communication[5] how these allylcarbonates can be used under Stoltz and Hong's conditions[26] for the diastereoselective Pd-catalyzed allylation.

Derivatization and sequential ACA–enolate trapping

In addition to the formal synthesis of terpenes described previously,[5] we attempted to derivatize a few representative adducts shown below. Starting from a mixture of diastereomers of the saturated ketone **14**, lactam **59** was formed in 35% overall yield using Beckmann conditions (Scheme 12).[27] The same strategy was envisaged for the synthesis of Baeyer–Villiger adducts **60** and **61** in 52 and 42% yield, respectively.[28] Both transformations offer a new approach to enantioenriched 4,5-disubstituted δ-lactam, 4,5-disubstituted δ-lactone, and 5,6-disubstituted ε-lactones. In all the cases, the initial *ee* values were recovered in the crude mixtures.

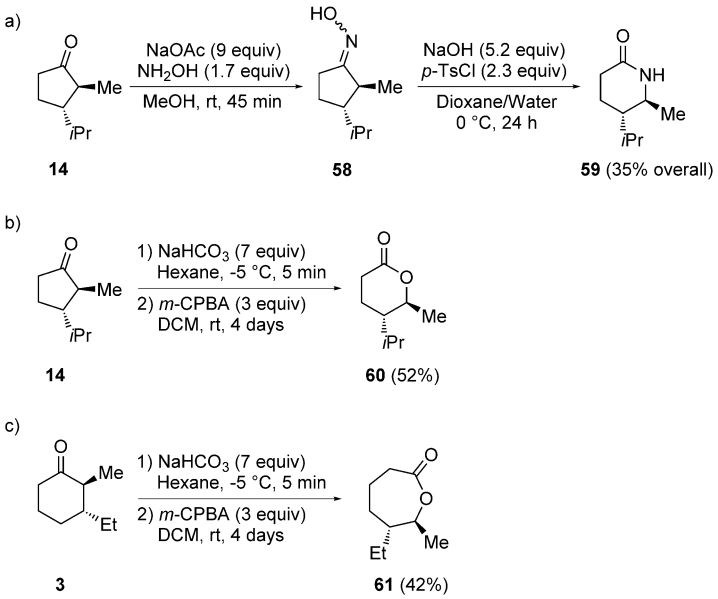
Triazoles have been widely explored by the chemical industry for the production of a new generation of fungicide. The development of antifungal drugs has been based on the same biological properties. Triazoles have also been associated with the concept of bioorthogonal chemistry.[29] By introducing a propargylic moiety, we now have access to the Huisgen cycloaddition procedure and thus to triazoles.[30] We have established that tosylazide was a suitable coupling partner for this transformation (Scheme 13). Ketones **32** and **33** were converted into the corresponding triazoles **62** and **63** in 71 and 68% yield, respectively.



Scheme 13. Application to the formation of triazoles.

Conclusion

The ACA to α-substituted cyclic enones is a tremendously important challenge in organic chemistry with a high synthetic potential. Our methodology, which is based on an easily prepared Mauduit-type NHC and a cheap copper salt, was shown to give access to contiguous tertiary centers in good *ee* values for a large scope of branched Grignard reagents. Our conditions were applied to six-membered rings as well. We then capitalized on the use of Grignard reagents and the intrinsically high reactivity of Mg–enolates to develop sequential ACA–enolate trapping. Hence, a large scope of highly functionalized substrates that bear contiguous quaternary and tertiary centers could be isolated in excellent d.r..[31] We eventually gained some insight into the synthetic potential of our substrates through several derivatizations. Our recent report that highlights the application of these findings in the formal total syntheses of bioactive diterpenes supports the versatility of the exposed methodology.



Scheme 12. Baeyer–Villiger and Beckmann reactions.

Experimental Section

All NMR spectroscopic measurements were recorded on a Bruker 500FT, Bruker 400FT, or Bruker 300FT instrument. The chemical shifts (δ) are indicated in parts per million relative to residual $CHCl_3$ ($\delta = 7.26$ ppm for 1H, $\delta = 77.16$ ppm for ^{13}C in $CDCl_3$). Coupling constants are given in hertz. Mass spectra (MS) were measured by means of electrospray ionization (ESI) and high-resolution mass spectra (HRMS) by means of ESI using the SMS service at the Université de Genève. Optical rotations were obtained using a Perkin–Elmer 241 or 341 polarimeter at 20 °C, $d = 10$ cm. Enantiomeric excesses were measured by means of chiral GC (HP6890 GC System, 10 psi H_2). Retention times (RT) are indicated in minutes. All commercial materials were used without further purification. All solvents were desiccated on a drying column of aluminum oxide under nitrogen. All the experiments were conducted using Schlenk techniques, and no glovebox was required to employ these synthetic methods.

General procedure for the ACA of Grignard reagents to α-substituted cyclic enones

A flame-dried flask was charged with NHC ligand and copper triflate. Dry diethyl ether (2 mL) was added and the suspension was stirred for 10 min at room temperature and 10 min at −30 °C. The Grignard reagent (solution in diethyl ether, 1.2 equiv) was then added and allowed to react over 30 min. The cyclic enone (1 equiv) was added with a syringe pump (15 min). The reaction was stirred for 4 h before acidic quenching with a solution of hydrochloric acid (1 M). The crude mixture was extracted with diethyl ether (three times). The organic phase was then washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The pure saturated ketones were isolated as colorless oils after silica gel flash chromatography.

General procedure to the ACA-enolate trapping sequence

Following the typical procedure for 1,4-addition, after 4 h, the crude mixture was diluted in dry tetrahydrofuran (1 mL) at −30 °C. Except for all the Michael reactions, the cyanations, the acetylations, and the carbonations, an excess amount of hexamethylphosphoramide (HMPA; 1 mL) was also required for improved yields. The resulting solution was allowed to stir for 30 min at −30 °C before the addition of the electrophile. After addition, the reaction mixture was allowed to warm overnight. The reaction was quenched with water, and the desired materials were isolated by following the same workup as that described above.

Acknowledgements

This work was supported by the Swiss National Research Foundation (grant no. 200020-126663).

Keywords: addition · copper · enantioselectivity · Grignard reagents · natural products

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Received: January 22, 2015
Published online on ■■ ▮▮, 0000

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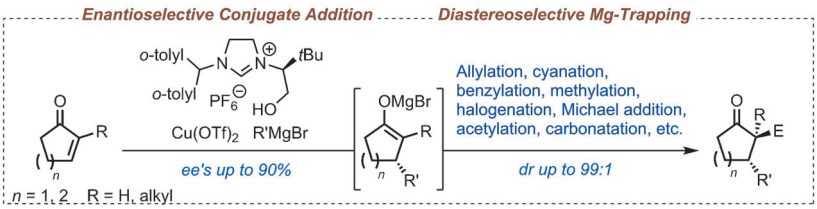

Adding machine: The asymmetric conjugate addition of Grignard reagents to 2-methylcyclopentone and -hexenone was achieved for the construction of multiple stereocenters up to 90% *ee*. In addition, the Mg–enolate can be trapped by various electrophiles. The present methods give access to synthetically versatile enantioenriched small molecules for natural product synthesis (see scheme).

Asymmetric Addition

*N. Germain, A. Alexakis**

■■ – ■■

Formation of Contiguous Quaternary and Tertiary Stereocenters by Sequential Asymmetric Conjugate Addition of Grignard Reagents to 2-Substituted Enones and Mg–Enolate Trapping