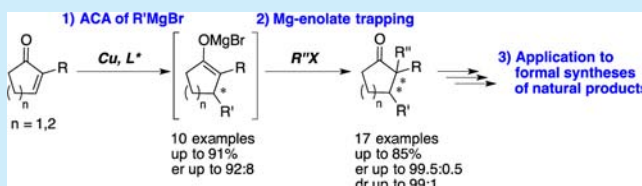


Asymmetric Conjugate Addition to α -Substituted Enones/Enolate TrappingNicolas Germain,[†] Laure Guénée,[‡] Marc Mauduit,[§] and Alexandre Alexakis^{*,†}[†]Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet, 30, 1211 Geneva 4, Switzerland[‡]Laboratory of Crystallography, University of Geneva, Quai Ernest Ansermet, 24, 1211 Geneva 4, Switzerland[§]Ecole National Supérieure de Chimie de Rennes, UMR 6226, Institut des sciences chimiques de Rennes - Equipe OMC, 11, allée de Beaulieu, Rennes 7, France

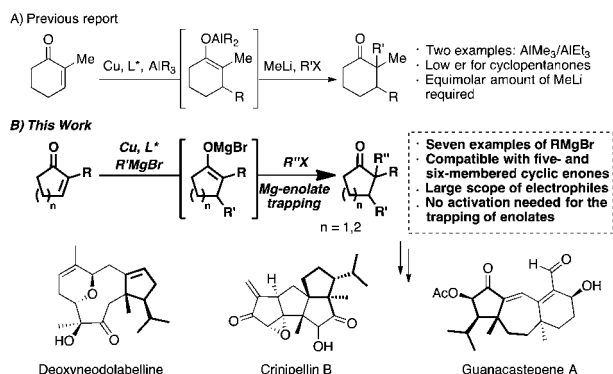
Supporting Information

ABSTRACT: An NHC–Cu complex catalyzed the asymmetric conjugate addition (ACA) of various Grignard reagents to nonactivated α -substituted cyclic enones to give 2,3-dialkylated cyclopentanones and cyclohexanones. The Michael addition features the formation of a magnesium enolate intermediate. One-pot diastereoselective trapping of this enolate by alkyl, propargyl, allyl, and benzyl halides led to ketones with contiguous α -quaternary and β -tertiary centers.



The copper-catalyzed asymmetric conjugate addition (ACA) is a well-established technology to build carbon–carbon bonds.¹ While manifold methodologies dealing with the ACA to monosubstituted or β -disubstituted enones are reported, the particular case of α -substitution remains unexplored because of its lack of reactivity. To date, only one procedure was developed for 2-methylcyclohexenone using only trimethyl- and triethylaluminum (Scheme 1A).² However,

Scheme 1. Asymmetric Conjugate Addition to Enones



the extension to five-membered rings gave low selectivity. From those limitations, a general approach to face this particularly challenging Michael addition is needed. Mauduit-type copper(I)–*N*-heterocyclic carbene (NHC) complexes have shown potent catalytic activity for the transfer of various organometallic reagents.³ We thus considered using these catalysts to promote the addition of versatile Grignard reagents to various α -substituted enones. In addition, the tandem conjugate addition–enolate trapping is potentially a unique tool for regio- and diastereoselective α -alkylation of ketones. In

practice, the sequence still deserves further optimization. Concerning α -substituted enones, the first tests showed that benzyl bromides were unsuccessfully trapped by aluminum enolates: the low reactivity toward benzyl iodide can be circumvented by a stoichiometric addition of methyllithium.⁴ While racemic conjugate additions/trapping of lithium and magnesium enolates are largely documented, the one-pot asymmetric version received by far less attention.⁵ In our model, we envisioned that $A_{1,2}$ strain in the distorted 2-substituted cyclopentenyl enolate would bring the pseudoaxial isopropyl unit to shield one face of the enolate for the diastereoselective formation of ketones bearing two contiguous tertiary and quaternary centers.⁶

Due to their prevalence in natural products, developing a straightforward access to all-carbon quaternary centers is of great importance.⁷ The direct construction of ketones with α -quaternary centers is still a challenge, and except for two isolated works of Knochel et al. and Trost et al.,⁸ all of the methods rely on enolate chemistry.^{9–12} Nevertheless, only a few of those aforementioned strategies were applicable to 5-membered rings.

Herein, we disclose the first ACA of Grignard reagents to 2-substituted cyclopentenones and cyclohexenones followed by the trapping of the magnesium enolate by various electrophiles (Scheme 1B). A double-diastereoselective process in sequential two-step catalysis and application to the formal synthesis of natural products are also discussed.

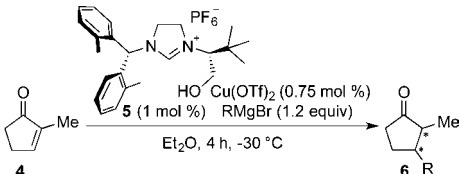
We first examined the reactivity of commercially available 2-methylcyclopentenone under different reaction conditions. After optimization, the *L*-tert-leucinol and di-*o*-tolylmethanamine-based Mauduit-type NHC ligand **5** was found to be

Received: October 29, 2013

Published: December 9, 2013

optimal for our study using only 0.75 mol % of catalyst loading.¹³ The scope of nucleophiles revealed that primary Grignard reagents were inferior to their branched counterparts (Table 1, entry 1 vs 2).

Table 1. Scope of Grignard Reagents for the ACA to 2-Methylcyclopentenone

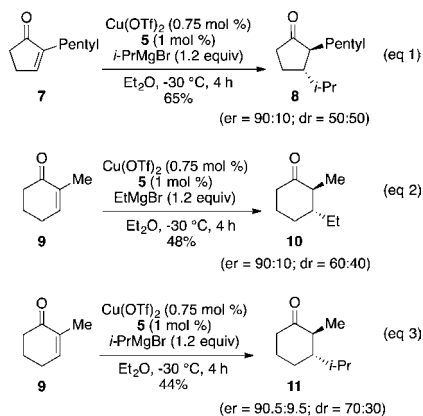


entry	product	R	yield ^a (%)	dr ^b	er ^c
1	6a	Et	75	81:19	80:20
2	6b	<i>i</i> -Pr	88	60:40	92:8
3	6c	3-pentyl	71	91:9	85.5:14.5
4	6d	5-heptyl	60	75:25	87:13
5	6e	<i>c</i> -pentyl	85	52:48	91.5:8.5
6	6f	<i>c</i> -hexyl	91	61:39	90:10
7	6g	<i>c</i> -heptyl	65	52:48	91.5:8.5
8 ^d	6b	<i>i</i> -Pr	90	60:40	92:8
9 ^e	6b	<i>i</i> -Pr	89	60:40	93.5:6.5

^a¹H NMR spectroscopy showed full conversion for all examples. ^bTrans/cis ratio. ^cSame er value for both diastereomers. ^dReaction scaled up to 3 mmol. ^eBatch of >3 M of *i*-PrMgBr.

We then explored the scope of Michael acceptors, and gratifyingly, 3-isopropyl-2-pentylcyclopentanone could be prepared in 90:10 er (Scheme 2).¹⁴ While primary Grignard

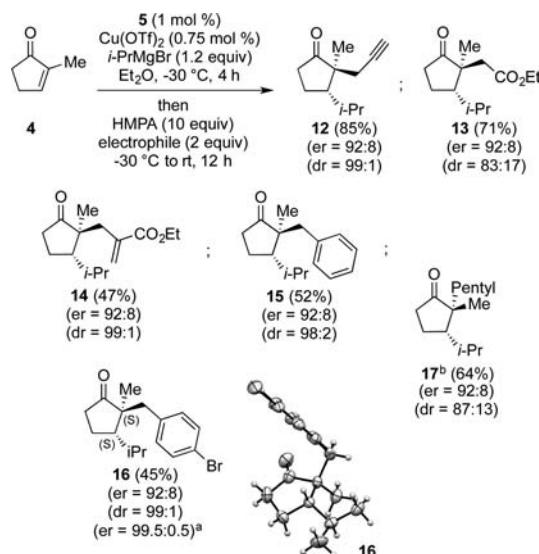
Scheme 2. Application to Other Michael Acceptors



reagents gave lower er for ACA to cyclopentenones, they were more efficient for the addition to 2-methylcyclohexenone. Indeed, we validated our concept for the addition of ethyl- and isopropylmagnesium bromide with, respectively, 90:10 er and 90.5:9.5 er.¹⁵ Since the trapping of the magnesium enolate by a proton gave moderate dr values (Table 1), we envisaged using other electrophiles (Scheme 3). The reaction of magnesium enolate with propargyl bromide,¹⁶ activated alkyl or allyl halides, and benzyl bromides yielded synthetically versatile adducts **12**–**16** in practical yields and diastereoselectivity up to 99:1 in favor of the *trans* adduct.

Remarkably, one-pot addition of methyl iodide to 2-pentyl-substituted enolate gave 3-isopropyl-2-methyl-2-pentylcyclopentanone **17**, the first example of enantioenriched 2,2,3-

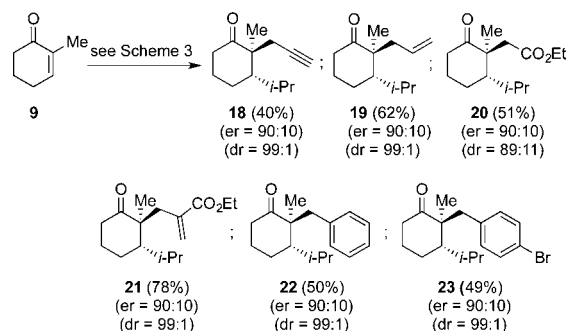
Scheme 3. Tandem ACA/Enolate Trapping to α -Substituted Cyclopentisopropylidenes^{a,b}



^aer after recrystallization. ^b7 instead of 4. X-ray crystal structures (ORTEP) of **16** (thermal ellipsoids shown at 50% probability).

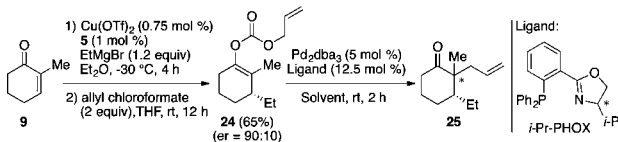
dialkylated cyclopentanone. As the X-ray structure of **14** suggests,¹⁷ a *trans* selectivity is observed. Analogously, we extended our reaction conditions to six-membered rings (Scheme 4). Diastereoselective formation of cyclohexanones proceeded with up to 99:1 dr using the same electrophiles as before.

Scheme 4. Tandem ACA/Enolate Trapping to α -Substituted Cyclohexenones



Since trapping of electrophiles led to *trans* adducts, a second chiral system is required to invert the selectivity and independently control the stereochemistry of the α -center. This sequence formally converts enantiomers to diastereomers, which are separable isomers. Two-step asymmetric catalysis is known, but only one displays double-diastereoselective processes as a second step.¹⁸ We thus decided to quench the magnesium enolate with allyl chloroformate. Racemic ACA followed by a racemic decarboxylative allylic alkylation gave 2:1 dr (see Scheme 3 and Table 2). This result was rather surprising since the comparison of eqs 2 and 3 in Scheme 2 indicates that a comparable level of diastereoselection can be reached for β -ethyl and β -isopropyl groups. Once quenched with HMPA and allyl iodide, magnesium enolate gave **19** in a perfect 99:1 dr while a 2:1 mixture was obtained with a Pd(η^3 -allyl) complex. Considering that allyl vinyl carbonates bearing a

Table 2. Double-Diastereoselective Decarboxylative Allylic Alkylation



entry	solvent	ligand	conv ^a (%)	dr ^b	er ^c
1	THF	R	100	90:10	96:4
2	toluene	R	82	93:7	97:3
3	toluene	S	100	42:58	99.5:0.5

^aConversion measured by ¹H NMR spectroscopy. ^bTrans:cis ratio. ^cer value of the major diastereomer.

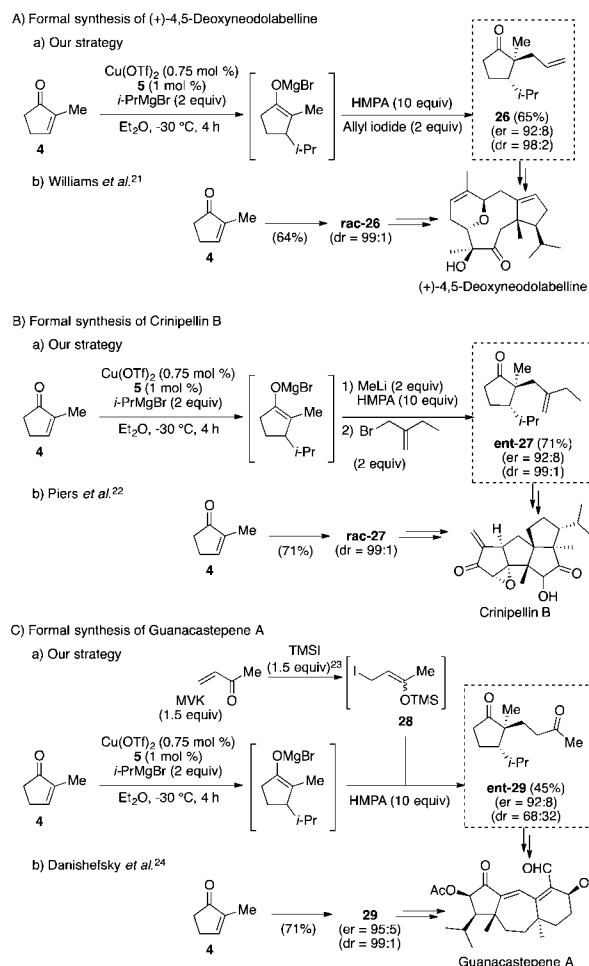
stereocenters like **24** have not been explored yet, we decided to apply the methodology developed by Stoltz et al. In the constructive case, chiral allyl vinyl carbonate **24** was smoothly converted to ketone **25** (96:4 er, 90:10 dr) in the presence of PHOX ligands and tris(dibenzylideneacetone)dipalladium(0) (Table 2).^{12,19}

The reaction was quantitative in THF using (R)-i-Pr-PHOX. In toluene, the reaction gave slightly higher enantioselectivity (97:3) and diastereoselectivity of 93:7 (entry 1 vs 2).²⁰ We logically tested the other enantiomer (S)-i-Pr-PHOX, and we were pleased to observe a total conversion and 42:58 dr in favor of the *cis* adduct. In this destructive case, the major *cis* diastereomer was measured in 99.5:0.5 er.

We eventually turned our attention to the formal synthesis of natural products. Our sequence offered a concise alternative route for the preparation (+)-4,5-deoxyneodolabelline or other neodolabellane skeletons starting from ketone **4**.²¹ Following the above-mentioned procedure, 2-allyl-3-isopropyl-2-methylcyclopentanone **26** can be synthesized using allyl iodide in 92:8 er and 99:1 dr (Scheme 5A). Another example of allyl halide has been attempted in the formal synthesis of tetraquinane diterpenoid crinipellin B.²² Our strategy using the same conditions as before, with 2-(bromomethyl)-1-butene as electrophile and stoichiometric addition of methyl lithium, allowed for the preparation of **ent-27** in good yield, 92:8 er, and 99:1 dr (Scheme 5B). Noteworthy, magnesium enolate can also be activated by methyl lithium even if no activation is essentially required for all the other examples showed in this communication. We then focused on a key intermediate of the synthesis of guanacastepene A.^{23,24} Since the direct trapping using methyl vinyl ketone (MVK) led to a complex mixture, we opted for a synthetic equivalent. Addition of trimethylsilyl iodide to MVK generated (4-iodobutenyloxy)trimethylsilane **28** in situ, which was reacted with the magnesium enolate.²⁵ The iodine of **28** is then displaced to afford 3-isopropyl-2-methyl-2-(3-oxobutyl)cyclopentanone **ent-29** in 92:8 er and 68:32 dr after acidic workup (Scheme 5C).

In summary, we have developed the first asymmetric conjugate addition of Grignard reagents to 2-substituted cyclic enones. The length of the aliphatic side chain and the ring size had little influence on the outcome of the methodology. Tandem ACA/enolate trapping was achieved to give contiguous α -quaternary β -tertiary centers in high er and dr. We also set up a multistep catalysis in order to produce *cis* and/or *trans* 2,2,3-trisubstituted cyclohexanones in high selectivity. Studies to extend the scope of this reaction as well as mechanistic considerations are currently underway in our laboratory.

Scheme 5. Application to the Formal Synthesis of Natural Products



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and complete characterizations (NMR spectra, GC and HPLC traces of both racemic and enantioenriched Michael adducts, IR, and HRMS). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Professor Clément Mazet and Professor Jérôme Lacour for helpful discussions.

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