Organic LETTERS

Letter

pubs.acs.org/OrgLett

Enantioselective Copper(I)-Phosphoramidite Catalyzed Addition of Alkylzirconium Species to Acyclic Enones

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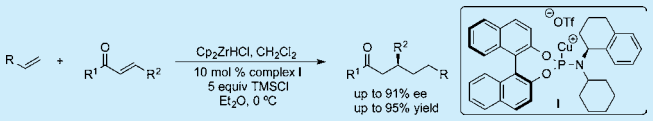
Supporting Information

ABSTRACT: Catalytic asymmetric conjugate addition reactions of alkylzirconium species to acyclic enones are reported. The alkylzirconium nucleophiles are generated in situ by hydrozirconation of alkenes with the Schwartz reagent. The reaction proceeds under mild and convenient conditions. A variety of functionalized nucleophiles can be used, and the method tolerates some variation in enone scope. The method uses a new chiral nonracemic phosphoramidite ligand in a complex with copper triflate.



The asymmetric conjugate addition (ACA) of organometallic species is a powerful way to make new carbon−carbon bonds.[1] While many methods have been developed, key challenges remain in terms of achieving acceptable reactivity and selectivity beyond a small number of model substrates. Obtaining high levels of enantioselectivity in ACAs to acyclic enones is more difficult than with cyclic enones. This is typically ascribed to *s-cis*/*s-trans* conformational interconversion (Figure 1a) occurring at a rate comparable to the reaction time

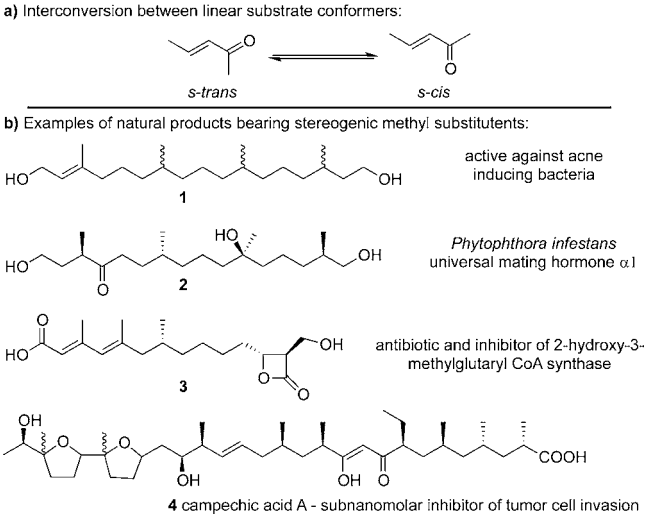


Figure 1. (a) Interconversion between *s-cis* and *s-trans* conformers in acyclic enones. (b) Examples of linear natural products bearing a stereogenic methyl substituent.

scale. Therefore, to obtain the desired ketone with high levels of enantioselectivity, the catalyst system must either be able to differentiate between these conformers or produce the same enantiomer product from both isomers.

Many natural products with important biological activity have a saturated alkyl chain featuring stereogenic centers. For example (Figure 1b), **1** is highly active against acne-inducing bacteria,[2] **2** is the universal mating hormone α1 of *Phytophthora infestans*, responsible for the Irish potato famine,[3] **3** is an antibiotic and specific nanomolar inhibitor of 2-hydroxy-3-methylglutaryl CoA synthase,[4] and campechic acid A (**4**) is a subnanomolar inhibitor of tumor cell invasion.[5]

There is a need to develop new reliable methods for the stereoselective construction of substituted linear alkanes, both for structure determination and for the synthesis of natural products and derivatives; the relative and absolute stereochemistry of **1**, for example, is not known. In the case of **2**, the combination of important biological activity and the difficulty of determining the relative and absolute configurations of stereogenic centers embedded in saturated alkyl chains have attracted considerable attention.[6]

Here, we report a copper-based system that is capable of catalyzing highly enantioselective additions of alkylzirconium species to noncyclic enones. The key to obtaining high enantioselectivity is the use of a new phosphoramidite ligand with a bulky chiral amido substituent. These reactions give linear chain ketones bearing a new stereogenic center.

Extensive research on Cu-catalyzed ACAs of premade alkylmetal species has provided several methods for addition of zinc,[7] aluminum,[8] and magnesium reagents[9] to linear enones (Figure 2), and boron reagents generated from alkenes can also be added to imidazol-2-yl α,β-unsaturated ketones.[10] We recently developed copper-catalyzed ACAs of alkylzirconium species (made by in situ hydrometalation of alkenes with the Schwartz reagent[11]) to a variety of cyclic acceptors.[12] These asymmetric additions of alkylzirconiums all use phosphoramidite ligands **B** or **D**, and we found that our previously developed systems give low levels of enantioselectivity in additions to acyclic Michael acceptors.

The hydrometalation of alkenes does not allow the addition of methyl nucleophiles, and so we chose to examine ACAs to

Received: January 4, 2015
Published: January 29, 2015

DOI: 10.1021/acs.orglett.5b00021
Org. Lett. 2015, 17, 912−915

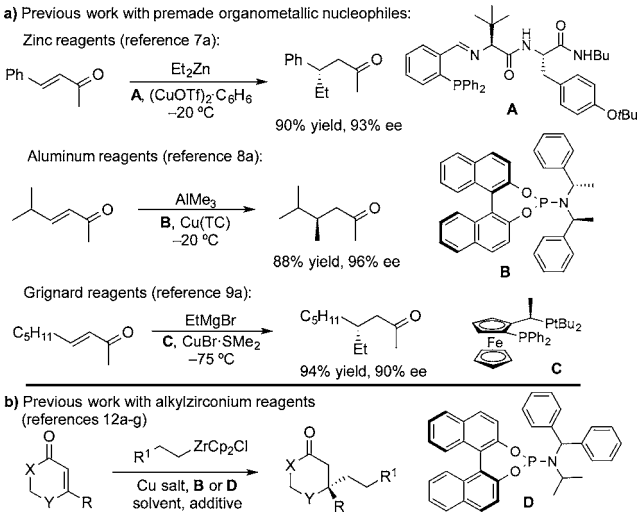
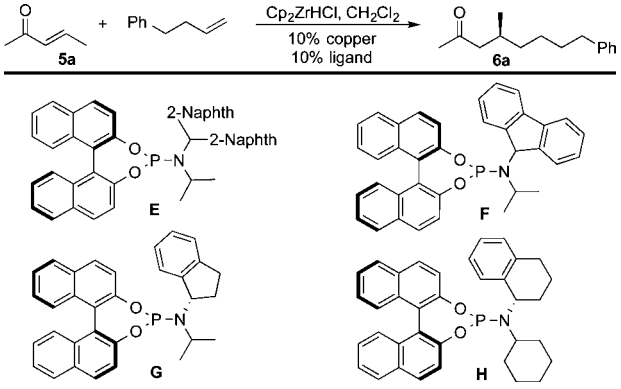


Figure 2. (a) Examples of asymmetric 1,4-additions to acyclic enones. (b) Previous enantioselective additions of alkylzirconium species are limited to cyclic electrophiles.

(*E*)-3-penten-2-one (**5a**) (Table 1). The addition of nonmethyl nucleophiles to **5a** would give chiral products such as **6a**, bearing a methyl group, a common feature of biologically active natural products. We point out that there are more readily available alkenes than acyclic enones, and so there may be advantages to methods where many different nucleophiles can, at least in principle, be added.

Previously developed conditions for ACAs to cyclic Michael acceptors were first examined, followed by variation of the ligand, copper salt, solvent, and additive (Table 1). The use of simple copper salts (such as Cu halides) in these reactions is ineffective (not shown). The use of copper triflimidate gave low enantioselectivity (entries 1 and 2), but copper triflate (made in situ from CuCl and AgOTf) gave 55% ee (entry 3), which could be improved to 60% ee (entry 4) by using TMSCl as an additive. Using the **D**-CuOTf-TMSCl combination with different solvents (entries 4–8) showed that dioxane and Et_2O give slightly better results (~64% ee). A variety of different ligands (for example, **E**–**H**, entries 9–12) were examined, and new phosphoramidite ligands **G** and **H** (see the Supporting Information) gave the highest levels of enantioselectivity (entries 11 and 12) with 88% and 89% ee, respectively. By varying solvent and temperature using ligand **H** (entries 13–16), ketone **6a** could be produced in 94% yield with 91% ee after 90 min at 0 °C (entry 16). Using ligand **H** in the absence of TMSCl (entry 17) gave the product with lower ee (79% ee). Isolated yields decrease if reaction times are extended; presumably, the product slowly degrades under the reaction conditions. Attempted optimization with ligand **G** (using a similar approach to that described above) did not lead

Table 1. Selected Optimization Reactions[a]



entry	copper source	ligand	solvent	additive	temp (°C)	ee (%)
1	CuCl + $AgNTf_2$	*ent*-**B**	*t*-BuOMe		rt	33
2	CuCl + $AgNTf_2$	**D**	*t*-BuOMe		rt	44
3	CuCl + AgOTf	**D**	*t*-BuOMe		rt	55
4	CuCl + AgOTf	**D**	*t*-BuOMe	TMSCl	rt	60
5	CuCl + AgOTf	**D**	THF	TMSCl	rt	38
6	CuCl + AgOTf	**D**	1,4-dioxane	TMSCl	rt	64
7	CuCl + AgOTf	**D**	Et_2O	TMSCl	rt	65
8	CuCl + AgOTf	**D**	CH_2Cl_2	TMSCl	rt	35
9	CuCl + AgOTf	**E**	Et_2O	TMSCl	rt	*ent*-71
10	CuCl + AgOTf	**F**	Et_2O	TMSCl	rt	*ent*-70
11	CuCl + AgOTf	**G**	Et_2O	TMSCl	rt	88
12	CuCl + AgOTf	**H**	Et_2O	TMSCl	rt	89
13	CuCl + AgOTf	**H**	1,4-dioxane	TMSCl	rt	85
14	CuCl + AgOTf	**H**	*t*-BuOMe	TMSCl	rt	89
15	CuCl + AgOTf	**H**	*t*-BuOMe	TMSCl	0	83
16	CuCl + AgOTf	**H**	Et_2O	TMSCl	0	91
17	CuCl + AgOTf	**H**	Et_2O		0	79

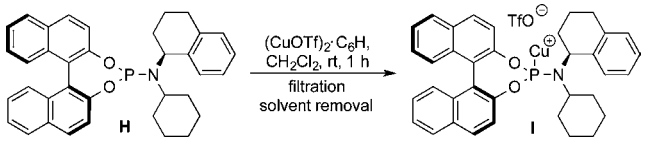
[a]Conditions: 4-phenyl-1-butene (2.5 equiv), Cp_2ZrHCl (2 equiv), (*E*)-pent-3-en-2-one (1 equiv), CuCl (0.1 equiv), silver salt (0.11 equiv), ligand (0.1 equiv), Additive (5 equiv), full conversion. Ee determined by HPLC.

DOI: 10.1021/acs.orglett.5b00021
Org. Lett. 2015, 17, 912–915

to improved results (not shown). Use of ligands **G** and **H** in addition to *cyclic* enones is less effective (by 10−20% ee) than using our previously reported conditions.[12]

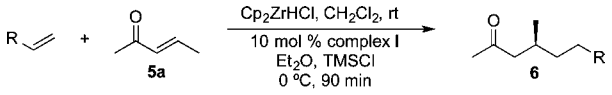
In order to simplify the experimental procedure, a solid precatalyst complex was made by mixing copper triflate benzene complex and **H** in dichloromethane at room temperature for 1 h. Filtration and removal of the solvent under vacuum (Scheme 1) gave solid complex **I** which is bench stable for at least 3 months when stored under argon.

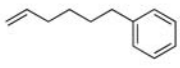
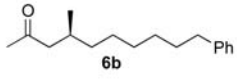
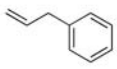
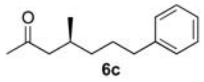
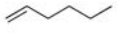
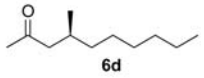
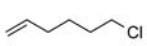
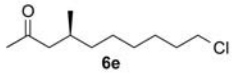
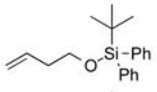
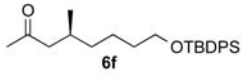
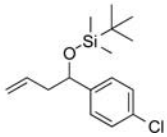
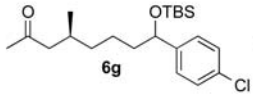
Scheme 1. Preparation of Precatalyst Complex I



Using the conditions developed above and **I**, different alkenes were examined in the hydrometalation−ACA to **5a** (Table 2). Generally, ketones **6** were obtained with good yields

Table 2. Asymmetric Addition of Alkyl Groups to 5a*



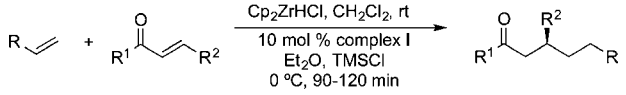
entry	starting alkene	product	yield[a]	ee[b]
1		 6b	73%	91%[c]
2		 6c	76%	91%[c]
3		 6d	90%	91%[d]
4		 6e	58%	*ca* 89%[d,e]
5		 6f	49%,	91%[c]
6		 6g	95%	91%[c,f,g]

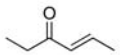
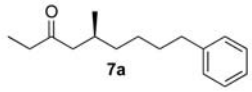
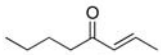
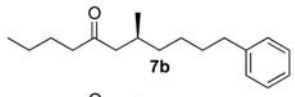
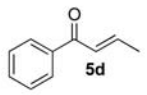
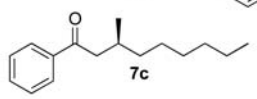
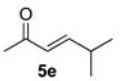
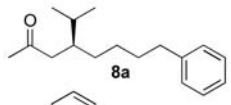
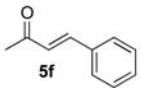
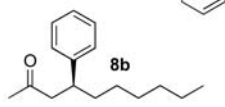
*Conditions: alkene (2.5 equiv), Cp_2ZrHCl (2 equiv), (*E*)-pent-3-en-2-one (1 equiv), complex I (0.1 equiv), TMSCl (5 equiv). [a]Isolated yield. [b]Absolute configurations known, determined, or assigned by analogy (see the Supporting Information). [c]ee determined by HPLC. [d]ee determined by GC. [e](±)-5% ee. Isolated as a 1:1 mixture of diastereomers. [g]ee determined by removal of the silyl group and HPLC.

and uniformly high enantioselectivity (usually 91% ee). The addition of 1-hexene gave known[8b] ketone **6d** (entry 3, 90% yield, 91% ee), and the absolute configurations of all products **6** are assigned by analogy to **6d**. Use of substrates bearing functional groups (entries 4−6) was examined. Chlorides **6e** and **6g** were both obtained with high ee (89−91% ee), although the enantiomeric excess of **6e** is difficult to measure precisely. Use of protected alcohols (entries 5 and 6) similarly gives ketone products with high enantioselectivity (91%). Overall, a variety of ketones, from those with simple alkyl chains (**6d**) to those with relatively complex structural units (**6g**), can be prepared with high enantiomeric excess.

We then investigated the enone scope, where the group adjacent to the carbonyl was varied (Table 3). When simple

Table 3. Asymmetric Addition to Additional Acyclic Enones*



entry	starting enone	product	yield[a]	ee[b]
1	 5b	 7a	94%	91%[c]
2	 5c	 7b	75%	91%[c]
3	 5d	 7c	66%	*ca* 80%[c,d]
4	 5e	 8a	59%	*ca* 66%[c,d]
5	 5f	 8b	59%	33%[c]

*Conditions: alkene (2.5 equiv), Cp_2ZrHCl (2 equiv), enone (1 equiv), complex I (0.1 equiv, TMSCl (5 equiv). [a]Isolated yield. [b]Absolute configurations known, determined, or assigned by analogy (see the Supporting Information). [c]ee determined by HPLC. [d](±)-5% ee.

primary alkyl groups were adjacent to the ketone (entries 1 and 2), products **7a** and **7b** were obtained in high yield with 91% ee. An enone with an aromatic ring next to the carbonyl (**5d**) also gave quite high enantioselectivity (about 80% ee) despite significant steric and electronic differences between **5a** and **5d**.

Enones **5e** and **5f**, bearing *β*-substituted *i*-Pr and phenyl groups, respectively (Table 3, entries 4 and 5), were then examined using the conditions optimized for substrate **5a**. The corresponding ketones were obtained with reasonable yields but lower enantioselectivity. These results suggest that the conditions developed above (Table 1) are not well suited for these bulkier acyclic enones (including chalcone, not shown), and new optimized conditions will be necessary to obtain **8a** and **8b** with high levels of enantiomeric excess.

In conclusion, a new method has been developed for Cu-catalyzed ACA of alkyl nucleophiles to acyclic enones. The nucleophiles are generated in situ from alkenes and the Schwartz reagent. The method tolerates wide variation in nucleophilic coupling partner. The enone scope is limited to acyclic enones bearing a primary (nonbranched) *β*-substituent. Further development, application, and mechanistic studies on this method are underway and will be reported in due course.

DOI: 10.1021/acs.orglett.5b00021
Org. Lett. 2015, 17, 912−915

■ ASSOCIATED CONTENT

Supporting Information

All procedures, characterization data, NMR spectra, and HPLC and GC traces. 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 the EPSRC for funding (Career Acceleration Fellowship to S.F. (EP/H003711/1)).

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DOI: 10.1021/acs.orglett.5b00021
Org. Lett. 2015, 17, 912−915