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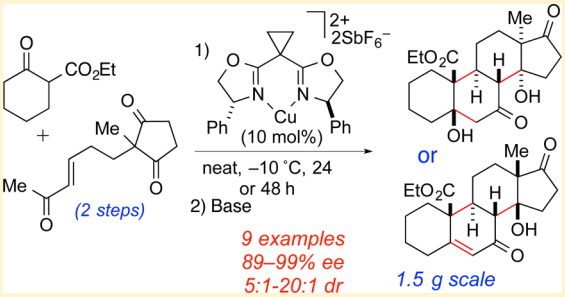
Concise Enantioselective Synthesis of Oxygenated Steroids via Sequential Copper(II)-Catalyzed Michael Addition/Intramolecular Aldol Cyclization Reactions

Nathan R. Cichowicz, Will Kaplan, Yaroslav Khomutnyk, Bijay Bhattarai, Zhankui Sun, and Pavel Nagorny*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

Supporting Information

ABSTRACT: A new scalable enantioselective approach to functionalized oxygenated steroids is described. This strategy is based on chiral bis(oxazoline) copper(II) complex-catalyzed enantioselective and diastereoselective Michael reactions of cyclic ketoesters and enones to install vicinal quaternary and tertiary stereocenters. In addition, the utility of copper(II) salts as highly active catalysts for the Michael reactions of traditionally unreactive β,β'-enones and substituted β,β'-ketoesters that results in unprecedented Michael adducts containing vicinal all-carbon quaternary centers is also demonstrated. The Michael adducts subsequently undergo base-promoted diastereoselective aldol cascade reactions resulting in the natural or unnatural steroid skeletons. The experimental and computational studies suggest that the torsional strain effects arising from the presence of the Δ^5-unsaturation are key controlling elements for the formation of the natural cardenolide scaffold. The described method enables expedient generation of polycyclic molecules including modified steroidal scaffolds as well as challenging-to-synthesize Hajos–Parrish and Wieland–Miescher ketones.



INTRODUCTION

Steroids play an important role in drug discovery, medicinal chemistry, and chemical biology. These compounds are responsible for the regulation of vital biological functions in animals and plants, and, not surprisingly, the steroidal scaffold is a privileged motif that is present in many FDA-approved drugs.[1] Developing means to access synthetic and natural steroids was one of the triumphs of last century's chemists, and the first total synthesis of a steroidal sex hormone, equilenin, by Bachmann dates back to 1939.[2] Despite major advances in the total synthesis of steroids, most steroid-based drugs are obtained by semisynthesis using feedstock isolated from plant or animal sources.[3] Recent developments in the field of asymmetric catalysis have enabled the efficient preparation of simple enantioenriched steroids such as estrones.[4] However, fewer asymmetric catalytic strategies for the construction of more complex steroids are available. In particular, despite the significant efforts invested in developing scalable synthetic routes to cardenolides, an asymmetric total synthesis of the steroids of this family still represents a formidable challenge.[4−7] Considering recent interests in developing safer versions of existing medicines as well as the growing demand for cardenolide-based therapeutics, a concise, scalable, and modular synthetic route to the cardenolide skeleton bearing necessary functionalization is highly desired.[5]

This Article describes a conceptually new asymmetric approach to steroids that enables rapid stereoselective synthesis of various cardenolide scaffolds. This approach relies on tandem asymmetric diastereoselective Michael addition/intramolecular aldol reactions to achieve expedient assembly of steroids.[8−10] It requires simple and readily available building blocks **5** and **6**, and achieves the synthesis of functionalized steroidal core **9** and the C13, C14-epimeric core **8** in only 4−5 steps (Figure 1).

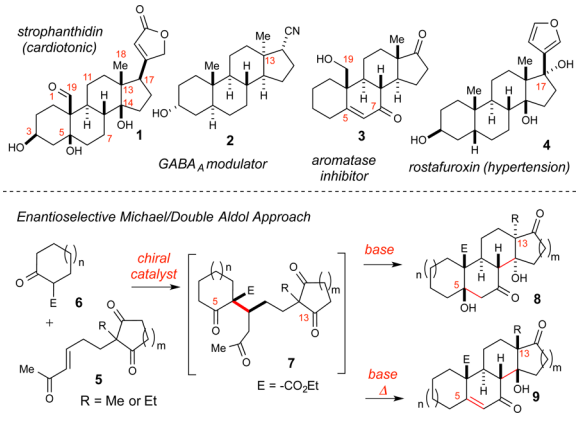


Figure 1. Approach summary.

In addition, our method tolerates modifications in **5** and **6**, which allows accomplishing rapid alterations in the ring size and

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C13-substituents of **8** and **9**. The scaffolds **8** and **9** are present in a variety of bioactive steroids (i.e., **1**−**4**, Figure 1), and their quick generation provides exciting opportunities for the synthesis of these and many other natural and unnatural diterpenes.

Finally, the formation of the sterically strained chiral Michael adducts is described using a new variant of Cu(II)-catalyzed Michael reactions under solvent-free conditions. Unprecedented Michael reactions with unreactive enones and ketoesters were achieved under these conditions, and applied to the preparation of chiral products with vicinal all-carbon quaternary centers and with vicinal quaternary and tertiary stereocenters. The development of this transformation not only enabled the four-step assembly of steroids, but also the asymmetric synthesis of functionalized Hajosh−Parrish and Wieland−Miescher ketones that are challenging to generate using existing methods.

RESULTS AND DISCUSSION

Initial Studies on Michael Reaction. As the asymmetric Michael reaction resulting in **7** is key to this approach, our studies commenced with investigating the addition of ketoester **6a** to enone **5a** (Table 1). Intermolecular Michael reactions of 2-substituted β-ketoesters and β-substituted enones resulting in vicinal quaternary and tertiary stereocenters are challenging.[11−13]

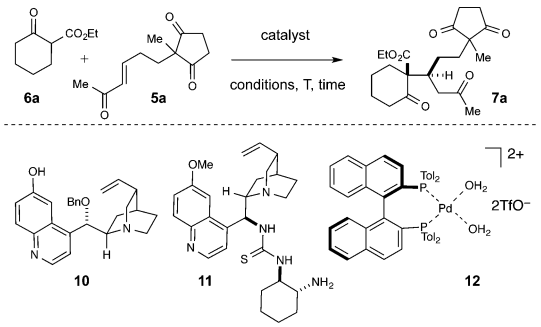
To date, only the asymmetric catalytic transformations developed by Sodeoka's, Wang's, Ye's, and Deng's groups describe the formation of these motifs with sufficiently high levels of enantiocontrol.[14] However, the evaluation of the aforementioned methods using catalysts **10**−**12** (Table 1)[12] did not result in significant formation of **7a**, probably due to the substantially lower reactivity of unactivated six-membered β-ketoester **6a**. While catalyst **12** could indeed promote the previously reported reaction of **6a** and methyl vinyl ketone to provide the corresponding Michael adduct in 77% yield, 36% ee (cf., Supporting Information), only 6% of **7a** was detected by ^{1}H NMR analysis of the crude mixture after 72 h when ketone **5a** was employed as an electrophile (entry 3).

Considering that the prior methods were not suitable for the approach outlined in Figure 1, our further attempts were focused on identifying a new, more reactive catalytic system. Our initial efforts to form **7a** with amine bases (entries 4−5) or LHMDS (not shown) were unsuccessful. However, in the following screening of the Lewis acid-based catalysts (entries 6-8), we discovered that $Cu(OTf)_2$ can promote an efficient Michael reaction[15] between **6a** and **5a** in 86% yield, 4:1 dr (Table 1, entry 8), under solvent-free conditions.[15e] Interestingly, $Cu(OTf)_2$ was unique in catalyzing the formation of **7a**. Thus, $Zn(OTf)_2$ (entry 6) did not promote any reaction, and the use of $Sc(OTf)_3$ (entry 7) led to decomposition of the starting materials. Furthermore, the diastereoselectivity of the $Cu(OTf)_2$-catalyzed reaction could be increased without affecting the yield if the reaction was run at 0 °C (entry 9).

Developing Asymmetric Variant of Michael Reaction. With the racemic variant of this reaction in hand, we investigated the enantioselective variant of this transformation by employing chiral Cu(II) Box and PyBox complexes (Table 2).[17] Such complexes have been previously employed as the catalysts for the conjugate additions of carbon and oxygen-based nucleophiles[17] as well as Mukaiyama Michael reactions.[18] The attempts of utilizing Cu(II) Box complexes for the direct Michael reactions of 1,3-dicarbonyls and enones are also documented;[19] however, racemic products were observed in such cases. Thus, the only successful example of enantioselective Michael reaction catalyzed by Cu(II) Box complexes relied on activation of chelating electrophiles such as β,γ-unsaturated α-ketoesters.[20]

The optimization results for the enantioselective reaction of **6a** and **5a** resulting in chiral **7a** are summarized in Table 2. While $Cu(OTf)_2$ complexes in some cases were found to promote enantioselective reaction (entries 1 and 11), the complexes with noncoordinating counterions were found to be more reactive (i.e., entry 1 vs entry 2). Extensive evaluation of various Box and PyBox ligands helped to identify

Table 1. Initial Evaluation of the Conditions for the Formation of Michael Product 7a



entry	catalyst	catalyst, mol %	conditions	T, °C	time, h	conversion (yield), %[a]	dr
1	**10**	20	1 M in CH_2Cl_2	rt	87	0	
2	**11**	10	1 M in PhMe	rt	72	0	
3	**12**	5	4 M in THF	0	72	6	
4	Et_3N	1000	0.4 M in MeCN	rt	48	0	
5	DBU	100	4 M in THF	rt	72	−[b]	
6	$Zn(OTf)_2$	10	neat	rt	3	0	
7	$Sc(OTf)_3$	10	neat	rt	3	−[b]	
8	$Cu(OTf)_2$	10	neat	rt	3	>95 (86)	4:1
9	$Cu(OTf)_2$	10	neat	0	4	>95 (81)	8:1

[a]These reactions were performed on 0.24−0.77 mmol scale with 1 equiv of **5** and **6**, and the catalyst of choice (10 mol %). The isolated yields that represent the average of two runs are provided. [b]Numerous side-products resulting from the decomposition of **5a** were detected.

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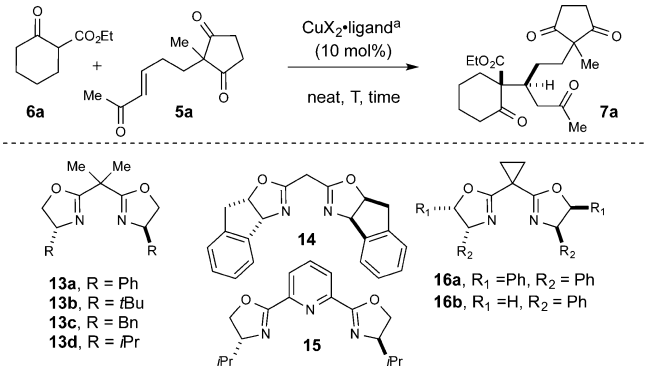
Table 2. Optimization of the Conditions for the Enantioselective Michael Reaction[a]



entry	ligand	CuX_2	*T*, °C	time, h	conversion (yield), %	dr	ee, %
1	**13a**	$Cu(OTf)_2$	rt	3	90 (83)	2.5:1	74
2	**13a**	$Cu(SbF_6)_2$	rt	3	>95 (88)	2.5:1	74
3	**13b**	$Cu(OTf)_2$	rt	3	0		
4	**13b**	$Cu(SbF_6)_2$	rt	3	0		
5	**13c**	$Cu(OTf)_2$	rt	3	0		
6	**13c**	$Cu(SbF_6)_2$	rt	3	0		
7	**13d**	$Cu(SbF_6)_2$	rt	3	>95 (96)	2.5:1	26
8	**14**	$Cu(SbF_6)_2$	rt	3	n.d.	n.d.	8
9	**15**	$Cu(SbF_6)_2$	rt	3	n.d.	n.d.	10
10	**16a**	$Cu(SbF_6)_2$	rt	3	>95 (71)	3:1	76
11	**16b**	$Cu(OTf)_2$	rt	3	>95 (88)	4:1	72
12	**16b**	$Cu(SbF_6)_2$	rt	3	>95 (93)	5:1	84
13	**16b**	$Cu(SbF_6)_2$	−10	48	>95 (89)	5:1	92
14	**16b**	$Cu(SbF_6)_2$	−20	72	80	6:1	93

[a]These reactions were performed on 0.24−0.6 mmol scale with 1 equiv of **5a** and **6a**, and the catalyst of choice (10 mol %). The isolated yields that are calculated on the basis of the average of two runs are provided. The dr is determined by ^{1}H NMR analysis, and the minor diastereomer of **7a** was isolated and characterized (cf., Supporting Information).

2,2′-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole)-ligand **16b** as the ligand of choice.[21] Substantial ligand effects were observed in these studies, and no reaction was observed with Box ligands **13b** and **13c** despite our numerous attempts to optimize these reactions. The copper(II) hexafluoroantimonate complex of **16b** promoted the formation of **7a** at rt in 93% yield and good selectivity (5:1 dr, 84% ee). The enantioselectivity of this reaction was improved at lower temperature (entries 13 and 14), and under the optimal conditions (entry 13) the desired Michael adduct **7a** was obtained in excellent yield and selectivity (89% yield, 5:1 dr, 92% ee).

As the possibility of introducing substituents at the C13 position and changing A/D ring sizes in **7** is key to the approach outlined in Figure 1, the substrate scope of the enantioselective Michael reaction was investigated next (Scheme 1). With five-membered *β*-ketoesters, the reactions proceeded significantly faster (24 h) and with higher levels of diastereocontrol (**7b**, **7c**, **7f**, **7g**). For both five- and six-membered ketoesters, the alterations in the *β*-substituent of *α*,*β*-unsaturated ketone portion of **5** were well tolerated, and substrates **7a**−**7i** were obtained in good yields, and with good diastereo- and enantioselectivities.

Remarkably, the introduction of the vinyl chloride moiety into six-membered ketoesters was also tolerated, and the corresponding vinyl chloride-containing Michael adduct **7i** was generated in excellent yield and selectivity. The presence of unsaturation resulted in significant enhancement in the dr of this reaction as a 14:1 mixture of diastereomers of **7i** was obtained. The absolute and relative configurations of these adducts were later confirmed by X-ray crystallographic analysis of their cyclized products (Schemes 4 and 5). Thus, the absolute configuration of the series of Michael adducts **7** depicted in Scheme 2 can be achieved with (*R*,*R*)-**16b**. Importantly, getting access to **7a**−**7i** in a highly selective manner was key to our synthetic plan outlined in Figure 1 and allowed us to further pursue the enantioselective synthesis of steroid analogues (Table 3).

The observations summarized in Table 1 suggest that Cu(II) salts are among the most active catalysts for the formation of sterically strained Michael adducts such as **7a** under solvent-free conditions. To further demonstrate this point, Michael adducts **7j** and **7k** with vicinal all-carbon quaternary stereocenters were generated in good yields using **16b** as the catalyst (Scheme 1). Because of the presence of unfavorable steric repulsions with the second *β*-substituent of the enone, these adducts were formed in lower enantioselectivities, and further optimization of the ligand would be required. At the same time, the ability to generate **7j** and **7k** using this method is of great utility by itself, considering that the formation of such Michael adducts with vicinal quaternary stereocenters is unprecedented under normal conditions, and the only existing reports describing similar transformations utilize stoichiometric base at ultra high pressures (15 kbar).[16]

The proposed mechanism of Cu(II)-catalyzed Michael reaction is provided in Figure 2. Thus, Cu(II) undergoes chelation with the enol form of *β*-keto-ester **6a** to provide complex **I**. Such complexes have previously been detected by

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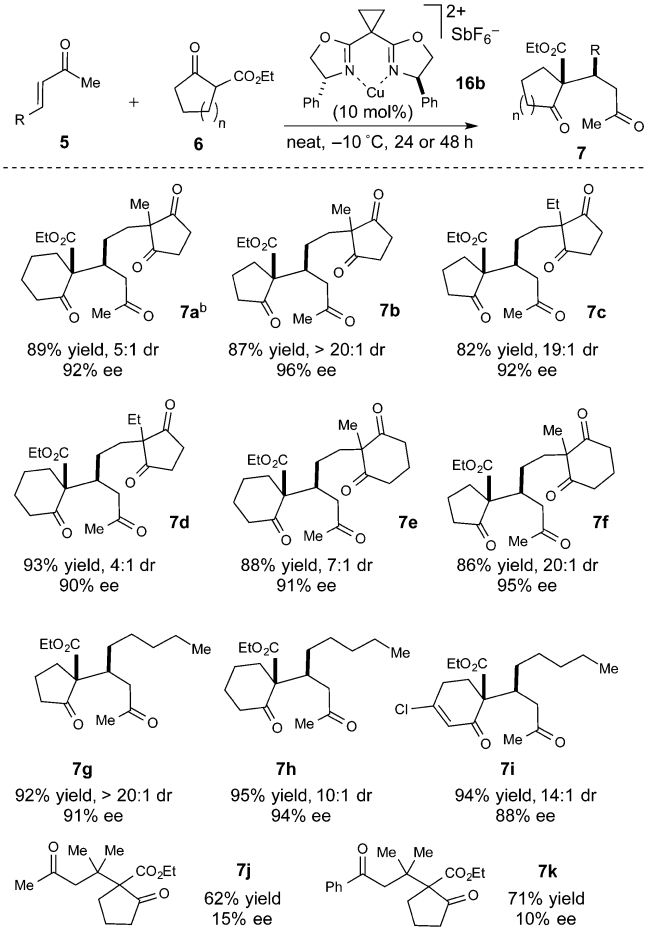
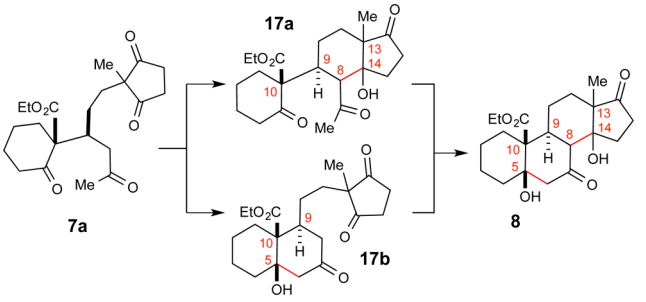
Scheme 1. Substrate Scope of the Enantioselective Michael Reaction[a]



[a](a) Reactions were performed on 0.82−1.3 mmol scale. The depicted absolute stereochemistry of **7a**−**7h** could be achieved with (*R*,*R*)-**16b**. The yields and selectivities represent an average of two runs. The dr is determined by ^{1}H NMR analysis. (b) This reaction was also performed on 10.8 mmol scale (cf., Scheme 5 and the Supporting Information).

Scheme 2. Proposed Double Cyclization Strategy



ESI MS and proposed to be active complexes in Cu(II)-catalyzed Michael reactions.[19a] This complex undergoes a Michael reaction with enone **5** to provide complex **II**. While some additional studies are required to clarify the details for the formation of complex **II**, coordination of **5** to Cu(II) followed by an intramolecular conjugate addition are proposed to be involved. The zwitterionic complex **II** then undergoes a proton transfer to generate complex **III**, which upon decomplexation regenerates **16b**.

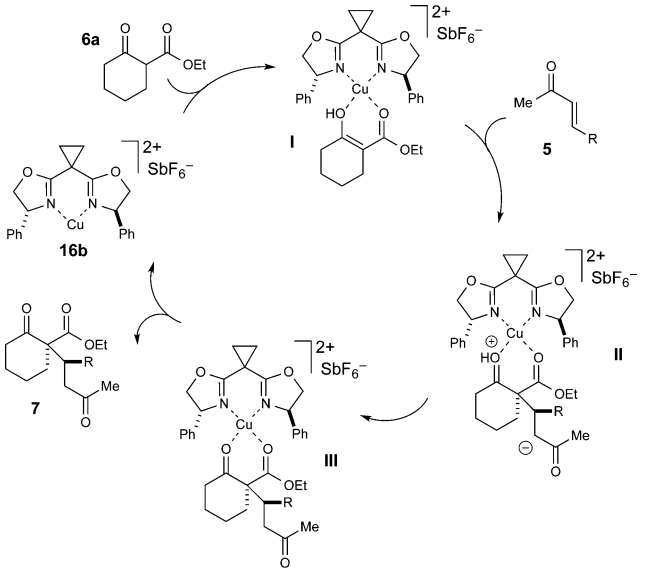
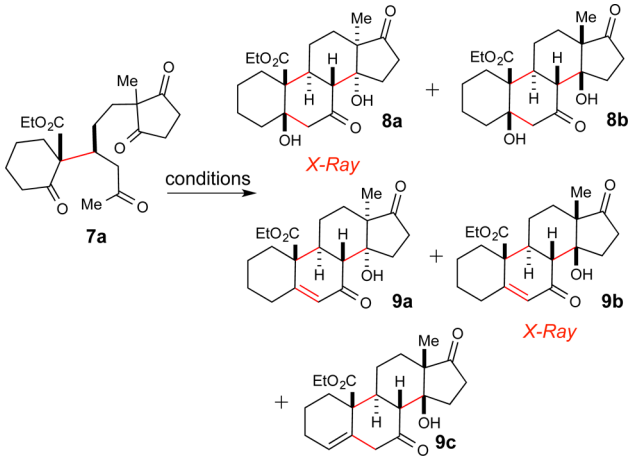


Figure 2. Tentative mechanism of Cu(II)-catalyzed Michael reaction.

Table 3. Double Aldol Cyclization Studies[a]



entry	conditions	conversion, % (yield, %)	products	selectivity
1	D- or L-proline DMF, rt, 24 h	0		
2	$TiCl_4$, Et_3N THF, −78 to 0 °C	decomposition		
3[b]	*p*-TSA, toluene reflux, 18 h	>98	**9a**	only
4	DBU, THF reflux, 18 h	>98 (94)	**8a**	only
5	piperidine, THF, reflux, 18 h	>98	**8a**	only
6	piperidine, LiCl THF, reflux, 18 h	>98	**8a**, **8b**, **9a**, **9b**	10:8:43:39
7[c]	KHMDS (1 equiv), THF, rt, 24 h	>98	**8b**, **9a**, **9b**	35:50:15
8[c]	KHMDS (2 equiv), THF, reflux, 30 min	>98 (48)	**9b**, **9c**	1:2
9	Cs_2CO_3, DMF, 140 °C, 1 h	>98 (89)	**9b**	only

[a]Prepurified diastereomerically pure **7a** was used for these studies. [b]Unidentified product (ca. 30%) was formed along with **9a**. [c]Significant amounts of retro-Michael reaction products were observed.

Double Aldol Cyclization Studies. With this key bond formation achieved, the double aldol cyclization strategy (Scheme 2) was investigated next. Depending on the sequence of the cyclization events, the formation of **8** from Michael

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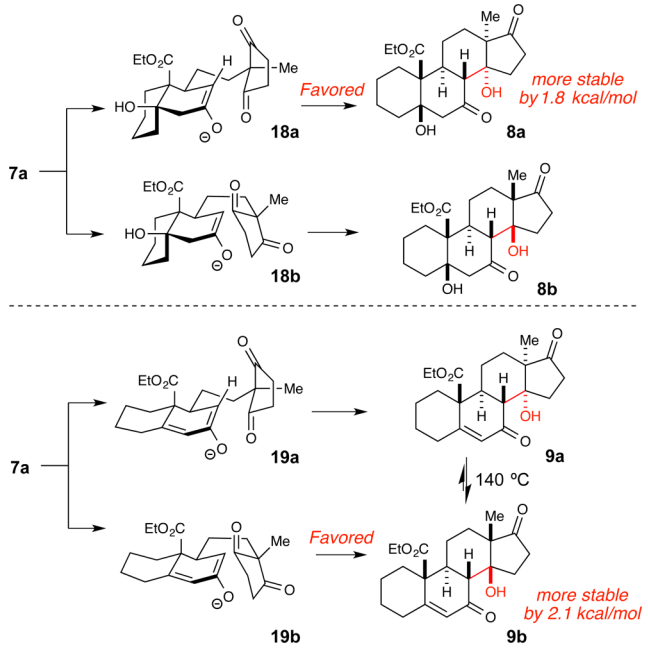
adduct **7a** can proceed via two different intermediates (i.e., **17a** and **17b**). It is noteworthy that the formation of steroid **8** results in four new stereogenic centers at the C5, C8, C13, and C14 positions. While the configuration of the C5 carbon will most likely be dictated by the adjacent C10 stereocenter regardless of the reaction pathway (i.e., **17a** vs **17b**), the perspectives of achieving control over the configuration of the three remaining centers were not as clear.

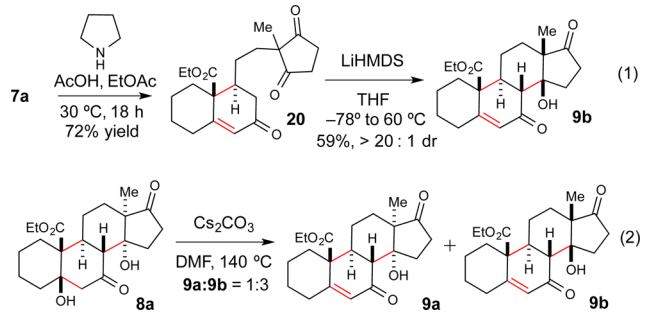
Moreover, the precedents established by the Deslongchamps group[6b] suggest that if the aldol cascade proceeds through **17b**, then the unnatural α-configuration of the C13 and C14 stereocenters is most likely to be formed (i.e., pro-*R* ketone attack in **17b** is preferred).

However, with no other precedents for the cyclization of **7a** existing, we anticipated that the configuration at the C8, C13, and C14 carbons can be controlled with the proper selection of the aldolization conditions. Therefore, the following studies commenced with evaluation of various promoters and catalysts of aldol reactions (Table 3). The cyclization of **7a** was unsuccessful under proline-catalyzed (entry 1) or soft enolization (entry 2) conditions. However, under the acidic conditions, cyclization proceeded to provide enone **9a** with the unnatural α-configuration of the C13- and C14-stereocenters (entry 3). Similarly, DBU- and piperidine-promoted transformations resulted in a clean formation of **8a** (entries 4 and 5). The use of LiCl as an additive in combination with piperidine affected the outcome of this cyclization, and enones **9a** and **9b** were formed along with **8a** and **8b** (entry 6). In our further attempts to improve the formation of **8b** and **9b**, containing the desired natural stereochemistry, we investigated KHMDS-promoted cyclizations (entries 7 and 8). Remarkably, the temperature was found to be an important parameter, and when conducted in refluxing THF, only the natural β-diastereomers **9b** and **9c** were formed. To avoid deconjugation of **9b** into **9c** and to prevent retro-Michael pathway, a milder base, Cs_2CO_3, was employed at an elevated temperature (140 °C, DMF). These conditions resulted in a fast formation of the desired enone **9b** with the β-configuration of the C13- and C14-stereocenters of the CD-ring junction (entry 9).

Origins of Diastereodivergence in Double Aldol Cyclization. The results summarized in Table 3 indicate that in the case of the double aldol adducts **8a** and **8b**, there is a clear preference for the pathway leading to the unnatural diastereomer **8a** (Scheme 3). At the same time, elevated temperatures lead to the selective formation of natural diastereomer **9b** containing Δ^5-unsaturation. These results are consistent with the mechanistic pathway, in which the B-ring is closed first. In the case of the reactions catalyzed by DBU or *p*-TSA (entries 3 and 4), the second aldol addition proceeds through **18a** and **18b** and leads to **8a** or **8b**, and the pathway from **18a** to **8a** is energetically more favored. Indeed, computations (DFT, geometry optimization, B3LYP, 6-31+G*) suggest that **8a** is more stable than **8b** by 1.8 kcal/mol. However, the reaction promoted by Cs_2CO_3 at 140 °C (entry 9) is likely to proceed through a different mechanism, in which the intermediate aldol adduct **18b** undergoes elimination of water to form the corresponding aldol condensation product **20** (cf., eq 1). This product then cyclizes via **19a** and **19b** to form **9a** and **9b**. With the Δ^5-unsaturation, the natural configuration present in **9b** becomes more stable, and thus the pathway proceeding through **19b** becomes more energetically favored. The observed preference for **9b** can possibly be the result of not only kinetic, but also thermodynamic control. Consistent

Scheme 3. Explanation of Diastereoselectivity for the Formation of 8a−9b





with this proposal, the computational studies suggest that the energy of the enone **9b** with natural configuration is 2.1 kcal/mol lower than the energy of the unnatural enone **9a**. We propose that formation of the C5−C6 enone double bond in ring B results in increased torsional strain for the unnatural α-configuration, and for the diastereomeric enones **9a**/**9b**, the natural β-diastereomer **9b** becomes more stable.[6h]

To validate the mechanistic proposal above, the experiments depicted in eqs 1 and 2 were performed. Enone **20** was prepared by pyrrolidine-promoted monocyclization of **7a**. This compound was treated with LiHMDS, which produced **9b** as the only observed product (>20:1 dr after 30 min, eq 1). In an additional control experiment, diastereomerically pure adduct **8a** was treated with Cs_2CO_3 at 140 °C (eq 2). As expected, **8a** underwent elimination of water, and a 1:3 mixture of **9a**:**9b** was observed under the reaction conditions. The outcome of this experiment suggests that the formation of **9a** and **9b** may be reversible at 140 °C. However, considering that significant quantities of **9a** were observed along with **9b**, the exclusive formation of **9b** observed for the direct cyclization of **7a** (entry 9, Table 3) cannot be a sole result of the thermodynamically controlled isomerization of **9a** into **9b**.

Application to the Synthesis of Natural and Unnatural Cardenolides. The formation of unnatural steroids **8a**−**8g** from the corresponding Michael adducts (**7a**−**7f**) was investigated next (Scheme 4). On the basis of the results

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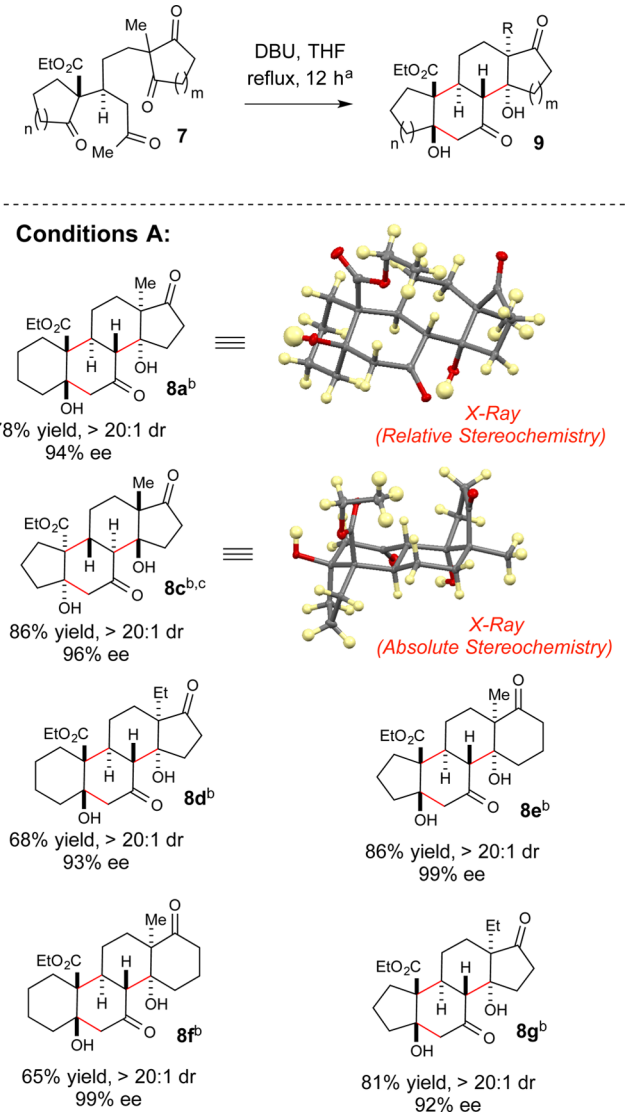
Scheme 4. Diastereoselective Formation of Steroids with Unnatural Configuration[a]

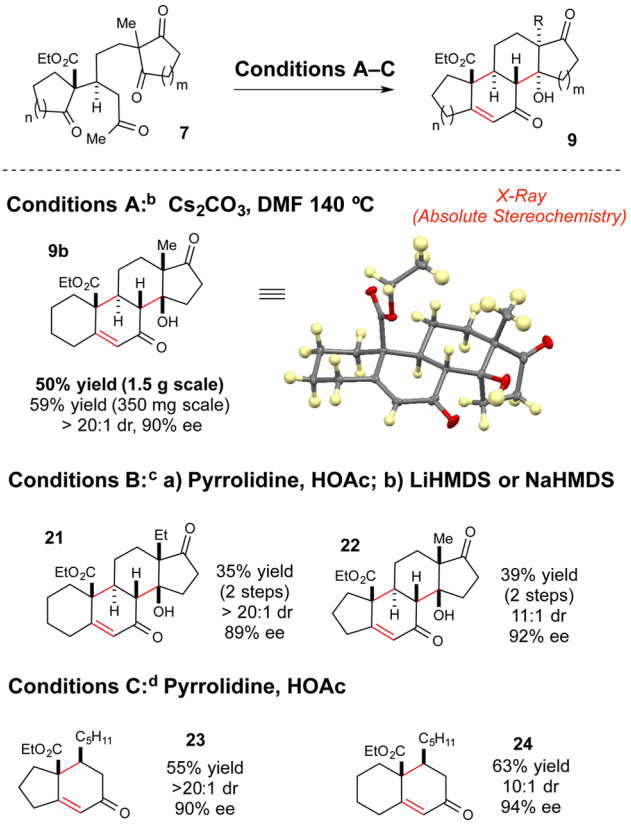


[a](a) Substrates **7** were used as the diastereomeric mixtures of Michael adducts (cf., Scheme 1) without preseparation of the minor diastereomers. Compounds **7** were treated with DBU, THF, reflux, 12 h. (b) The yields are reported for the isolated major diastereomer after purification by chromatography. (*R*,*R*)-Enantiomer of **16b** was used to generate the depicted enantiomers of **8**. (c) (*S*,*S*)-Enantiomer of **16b** was used to generate the depicted enantiomers of **8c**.

summarized in Table 3, DBU was selected as the base of choice to promote these cyclizations. Upon subjecting **7a**–**7f** to DBU in refluxing THF, the cyclizations proceeded cleanly and resulted in the formation of the corresponding steroids with the epimeric α-CD-ring junction. In all cases, the epimeric steroids were obtained in excellent yields and selectivities, and the formation of the otherwise challenging to generate by semisynthesis **8a**, **8d**, and **8e** as well as C13-ethyl group containing products **8c** and **8f** was successfully achieved. The relative configurations of compound **8a** and the relative and absolute configuration of **8d** were assigned on the basis of X-ray crystalographic analysis (cf., Scheme 4). It is also noteworthy that all of these compounds were generated via four-step linear sequences from the commercially available building blocks.

To demonstrate that our method could be used for the generation of steroids with natural cardenolide configuration, chiral steroid **9b**, as well as enones **21** and **22** were formed from the corresponding Michael adducts (conditions A and B, Scheme 5). It is noteworthy that the formation of **9b** was

Scheme 5. Diastereoselective Formation of Steroids with the Natural Configuration[a]



[a](a) Substrates **7** were used as the diastereomeric mixtures of Michael adducts (cf., Scheme 1) without preseparation of the minor diastereomers. The reactions were complete and the yields are based on the isolated diastereomerically pure **9b**, **21**–**24** after purification. Condition A: Cs_2CO_3, DMF, 140 °C, 1 h. (b) Condition B: (i) Pyrrolidine (1 equiv), AcOH (1 equiv), EtOAc, 30 °C, 20 h; (ii) LHMDS/THF (**21**) or NaHMDS/toluene (**22**), reflux. (c) Condition C: Pyrrolidine (1 equiv), AcOH (1 equiv), THF, 30 °C, 18 h.

carried out on a 1.5 g scale without significant erosion in yield and enantioselectivity, and its absolute and relative configurations were confirmed by X-ray crystallographic analysis. Compound **9b** possesses all of the necessary functionalities and stereochemistry to be converted to cardenolides as well as other steroids, and the efforts in this direction are ongoing in our laboratories.

A two-step protocol (condition B) was required for the clean formation of **21** and **22** as the corresponding cyclizations with Cs_2CO_3 at 140 °C resulted in significant amounts of retro-Michael products. To circumvent this problem, the Michael adducts **7b** and **7d** were monocyclized with pyrrolidine acetate (i.e., conditions resulting in the pre-formation of enamine) to afford a clean formation of the corresponding Δ^5-enones. As in the case of the cyclization described in eq 1, the following treatment of the monocyclized enone with LiHMDS (**21**) or NaHMDS (**22**) resulted in a clean diastereoselective formation

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of the corresponding cardenolide analogue with the natural configuration.

As a result, the corresponding steroids **21** and **22** were obtained in 35% and 39% yields (two steps), respectively, starting with the diastereomeric mixtures of the corresponding Michael adducts. Importantly, the semisynthetic methods based on the modification of the natural steroids would not provide a straightforward access to analogues such as **21** and **22**, while our current approach permitted an expedient generation of these scaffolds in only five steps from the commercially available starting materials.

Finally, the formation of substituted Hajosh–Parrish and Wieland–Miescher ketones,[22] by the cyclization of Michael adducts **7g** and **7h** (condition C), was performed to provide enones **23** and **24**. Such enones (and **24** in particular) contain adjacent quaternary/tertiary stereocenters and to our knowledge are not readily obtained enantioselectively.[23]

SUMMARY AND CONCLUSIONS

A new method for a rapid assembly of natural and unnatural cardenolide skeletons has been developed. This method is enabled by developing a new chiral bis(oxazoline) copper(II) complex-catalyzed enantioselective and diastereoselective Michael reaction of cyclic ketoesters and enones to install vicinal quaternary and tertiary C9- and C10-stereocenters. These products subsequently undergo base-promoted diastereoselective aldol cascade reactions resulting in the natural or unnatural steroid skeletons. The mechanistic studies suggest that the stereodivergence in the cyclization step arises from the torsional effects that favor a thermodynamically more stable natural configuration-containing ring system **9b** at the elevated temperatures. The described method enables expedient generation of polycyclic molecules including modified steroidal scaffolds and challenging-to-synthesize substituted Hajos–Parrish and Wieland–Mischer ketones. It is also noteworthy that the Cu(II)-catalyzed Michael reaction developed in these studies represents one of the most powerful transformations of this type displaying great tolerance to steric bulk of both nucleophiles and electrophiles. Thus, the work described herein suggests that this method is among the best asymmetric methods for the formation of the Michael adducts containing vicinal quaternary and tertiary stereocenters. In addition, the application of this new protocol allowed the unprecedented under normal conditions preparation of Michael adducts **7j** and **7k** containing vicinal quaternary stereocenters. The further application of this method to the synthesis of natural and unnatural steroids and diterpenes is the subject of ongoing studies in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08528.

Experimental procedures, and ^{1}H and ^{13}C NMR spectra (PDF)

X-ray data for compound **7a** (CIF)

X-ray data for compound **7b** (CIF)

X-ray data for compound **9b** (CIF)

AUTHOR INFORMATION

Corresponding Author

*nagorny@umich.edu

Notes

The authors declare no competing financial interest.

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