

Asymmetric Catalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201600235
Internationale Ausgabe: DOI: 10.1002/anie.201600235Iridium-Catalyzed Diastereoselective and Enantioselective Allylic Substitutions with Acyclic α -Alkoxy Ketones

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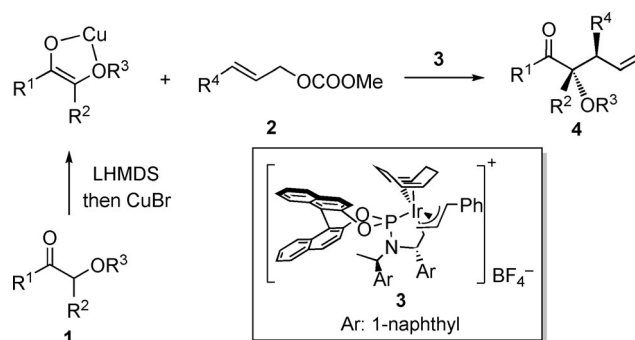
Abstract: The asymmetric alkylation of acyclic ketones is a longstanding challenge in organic synthesis. Reported herein are diastereoselective and enantioselective allylic substitutions with acyclic α -alkoxy ketones catalyzed by a metallacyclic iridium complex to form products with contiguous stereogenic centers derived from the nucleophile and electrophile. These reactions occur between allyl methyl carbonates and unstabilized copper(I) enolates generated *in situ* from acyclic α -alkoxy ketones. The resulting products can be readily converted into enantioenriched tertiary alcohols and tetrahydrofuran derivatives without erosion of enantiomeric purity.

Transition metal catalyzed asymmetric allylation of enolates serves as an efficient and reliable method to construct carbon–carbon bonds with high levels of asymmetric induction.^[1] The majority of these reactions form products containing a single stereocenter from either a prochiral enolate as the nucleophile or a prochiral allylic compound as the electrophile. If both nucleophile and electrophile are prochiral, synthetically valuable dyads containing contiguous stereocenters could be assembled in a catalytic and stereoselective fashion.^[2] However, this transformation is challenging because a new bond needs to be formed between two sterically hindered prochiral carbon atoms with control of both absolute and relative configurations.

Metallacyclic iridium complexes catalyze allylic substitutions with a variety of carbon and heteroatom nucleophiles regio- and enantioselectively.^[1b,3] Although reactions have been reported between prochiral enolates and prochiral electrophiles to afford products containing vicinal tetrasubstituted and trisubstituted stereocenters with excellent diastereo- and enantioselectivity, reactions with unstabilized, acyclic, prochiral ketones have not been reported.^[4] The main challenge facing this transformation results from the lack of control of the geometry of the unstabilized enolate of an α -branched acyclic ketone. In contrast to cyclic enolates, the backbone of the nucleophile does not dictate the geometry. Also, because α -branched, acyclic ketones do not readily form enamines, the use of amine auxiliaries has not been effective to control the geometry.^[5]

In the presence of suitable metal cations, acyclic carbonyl compounds bearing α -heteroatoms form enolates with a defined geometry created by chelation. This structure has been exploited for the allylation of glycine derivatives.^[6] However, these reactions occurred with low diastereoselectivity when forming products containing adjacent tetrasubstituted and tertiary stereocenters.^[6a] With the same strategy, Evans and co-workers achieved diastereoselective allylations of α -hydroxy, as well as α -alkoxy or α -siloxy acetophenone catalyzed by an achiral rhodium catalyst.^[7] However, only products containing adjacent tertiary and trisubstituted stereocenters, bearing an oxygen atom, were formed, and no enantioselective transformation was reported. We envisioned that this strategy could be used to achieve the enantioselective allylation of unstabilized ketones with cyclometallated iridium catalysts we developed.^[8]

Herein, we report diastereo- and enantioselective allylic alkylations with unstabilized enolates of acyclic α -alkoxy ketones catalyzed by the iridium complex **3** (Scheme 1). The geometry of the enolates is controlled through chelation in the presence of a copper(I) cation. These reactions form, with high diastereo- and enantioselectivity, products containing vicinal oxygen-bearing tetrasubstituted and tertiary stereocenters. Products containing a MOM (methoxymethyl) group on the tertiary alcohol were formed in good yield with high d.r. and *ee* values, and these products can be readily converted into tertiary alcohols and tetrahydrofuran (THF) derivatives without erosion of enantiomeric purity.

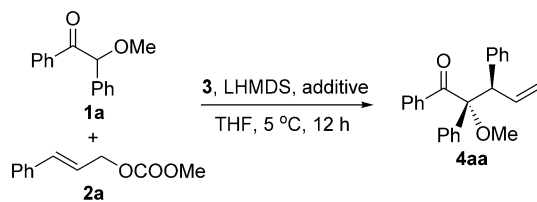


Scheme 1. Iridium-catalyzed diastereo- and enantioselective allylations with unstabilized copper(I) enolates of acyclic α -alkoxy ketones.

To assess the potential of developing an iridium-catalyzed allylation of an acyclic ketone enolate, we conducted the reactions between *O*-methyl benzoin (**1a**) and methyl cinnamyl carbonate (**2a**; Table 1). Treatment of **1a** and **2a** with **3** in the presence of LHMDS at 5 °C for 12 hours furnished the

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Table 1: Evaluation of reaction conditions for the iridium-catalyzed allylation.^[a]

Entry	Additive	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	–	95	2.0:1	n.d.
2	LiCl	> 99	1:1.1	n.d.
3	ZnCl ₂	72	16:1	n.d.
4	CuI	97	5.7:1	n.d.
5	CuCl	58	10:1	n.d.
6	CuBr	> 99 (> 99)	14:1	92
7	CuCN	34	2.5:1	n.d.
8	CuOAc	52	1.5:1	n.d.
9	CuSCN	94	2.3:1	n.d.
10 ^[e]	CuBr	42	2.7:1	n.d.
11 ^[f]	CuBr	> 99	14:1	93
12 ^[g]	CuBr	> 99	12:1	95
13	CuBr ₂	0	–	n.d.

[a] The molar ratio of **1a/2a/3/LHMDS/additive** = 2:1:0.02:2:2. The absolute configuration of **4aa** was assigned by analogy. [b] Combined yield of two diastereoisomers. Determined by ¹H NMR analysis with mesitylene as an internal standard. The yield within parentheses is that of the two diastereoisomers isolated. [c] Determined by ¹H NMR analysis of the crude reaction mixtures. [d] Determined by chiral-phase SFC analysis of the major isomer. [e] KHMDS was used as the base instead of LHMDS. [f] 1 equiv of CuBr was used. [g] 0.5 equiv of CuBr was used. LHMDS = lithium hexamethyldisilazide, n.d. = not determined, THF = tetrahydrofuran.

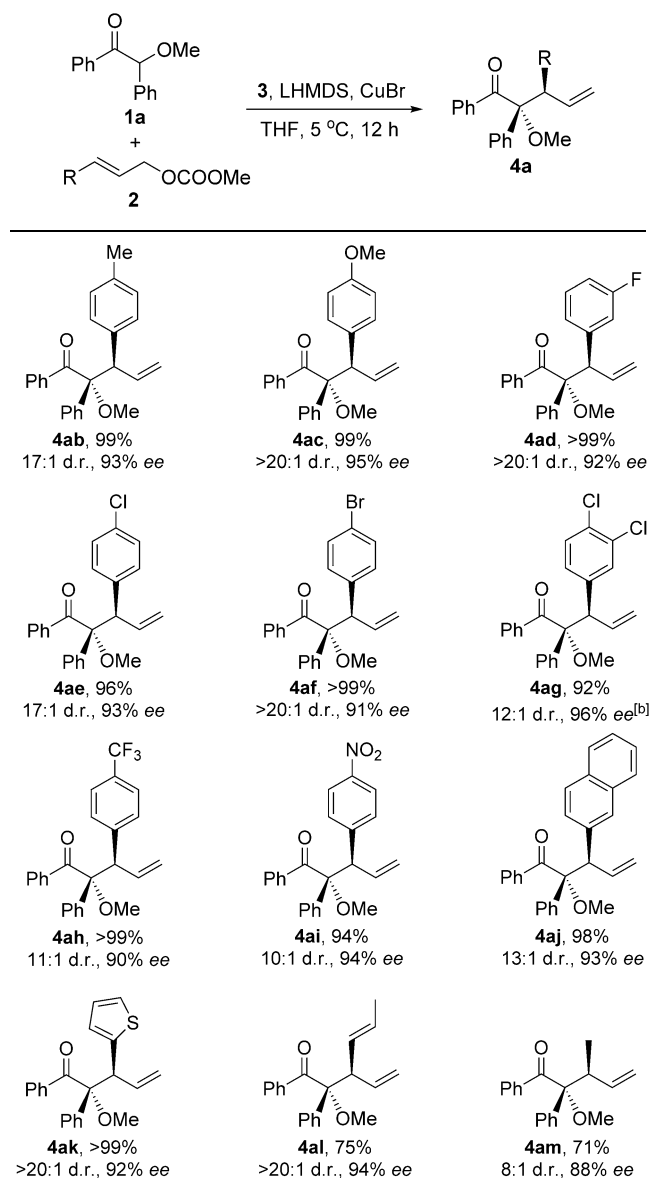
branched product **4aa** in 95 % yield (combined yield of two diastereoisomers), but with a low d.r. of 2.0:1 (entry 1). The reaction conducted after addition of LiCl^[40] to the lithium enolate gave the product with a lower d.r. of 1:1.1, slightly favoring the formation of the other diastereoisomer (entry 2). The reaction with added ZnCl₂^[6] afforded **4aa** with excellent diastereoselectivity (16:1 d.r., entry 3), albeit in a lower yield of 72 %. In contrast, the reaction conducted with added CuI occurred with a higher diastereomeric ratio of 5.7:1 while maintaining excellent conversion into **4aa** in a 97 % yield (entry 4). Similarly, Evans and co-workers observed higher diastereoselectivity with the copper(I) enolate of α -hydroxy acetophenone derivatives than with the corresponding lithium enolate.^[7a] Because the anion of the copper(I) salt could influence the transmetalation, we further evaluated a series of copper(I) salts. Reactions conducted with added CuBr occurred with a higher diastereomeric ratio of 14:1 with an excellent *ee* value of 92 % (Table 1, entry 6). The major diastereoisomer was isolated in 93 % yield (see the Supporting Information for details). Reactions with other copper(I) additives, such as CuCl, CuCN, CuOAc or CuSCN, occurred in significantly lower yield (58 %, entry 5) or with lower d.r. values (entries 7–9).^[9] The identity of the cation of the anionic base was crucial to obtaining high yields and diastereoselectivities. Reactions conducted with KHMDS instead of LHMDS afforded only 42 % yield of **4aa** with

a significantly lower d.r. of 2.7:1 (entry 10). Reactions conducted with one equivalent of copper in place of two equivalents led to excellent reactivity and afforded the product in identical d.r. and *ee* values (entry 11), but reactions with 0.5 equivalents occurred with a lower d.r. value (although slightly higher *ee*), as shown in entry 12.^[10] In all cases, the branched product was obtained exclusively. Reactions run with CuBr₂ as an additive gave no product, thus indicating the critical role of the copper(I) cation in this reaction, rather than a copper(II) cation which might be formed by disproportionation or oxidation of a copper(I) salt (entry 13).

The scope with respect to the allylic electrophiles which underwent the iridium-catalyzed allylic substitution with acyclic α -alkoxy ketones is summarized in Table 2. Various *para*-substituted cinnamyl carbonates are suitable electrophiles. Electron-neutral (**4ab**), electron-donating (**4ac**) and electron-withdrawing (**4ah**, **4ai**) functional groups on the cinnamyl aryl ring were all tolerated in this reaction, and the corresponding products were formed in excellent yield (\geq 94 %) with high d.r. (\geq 10:1) and *ee* values (\geq 90 %). Cinnamyl carbonates bearing halogens at either the *para*- or *meta*-position reacted cleanly, thus furnishing **4ad–ag** in greater than or equal to 92 % yield, 12:1 d.r., and 91 % *ee*.^[11] The absolute configuration of **4ag** was established by single-crystal X-ray diffraction.

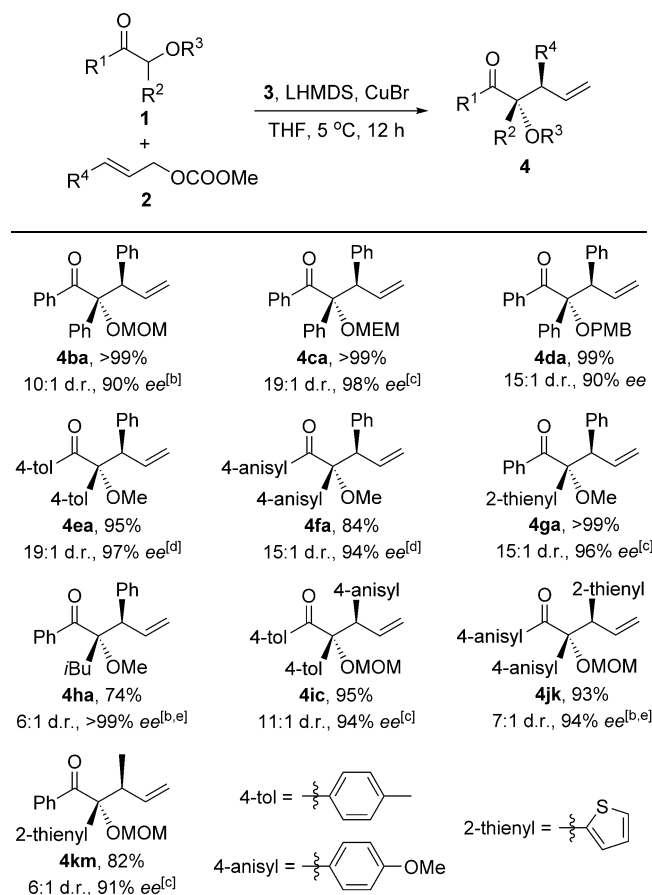
The reaction also occurred with allylic carbonates containing heteroaryl, alkenyl, and alkyl substituents. The reaction of the thienyl carbonate **2k** afforded **4ak** in high yield with excellent diastereo- and enantioselectivity ($>$ 99 %, $>$ 20:1 d.r., 92 % *ee*). Methyl sorbyl carbonate (**2l**) reacted to form the product **4al** in 75 % yield with greater than 20:1 d.r. and 94 % *ee*. Even the simple crotyl carbonate (**2m**) reacted to form product **4am** in good yield, although the d.r. and *ee* values were slightly lower than those with aryl-substituted allylic carbonates.

The scope of the acyclic α -alkoxy ketones that underwent the iridium-catalyzed allylation is summarized in Table 3.^[12,13] MOM- (**1b**), MEM- (methoxyethoxymethyl; **1c**), and PMB-protected (*para*-methoxybenzyl; **1d**) benzoin derivatives underwent allylation in high yield with excellent diastereo- and enantioselectivity. The reaction between **1b** and **2a** required a higher catalyst loading of 4 mol % to reach full conversion within 12 hours. Several acyclic O-Me benzoin derivatives bearing identical substituents at both aryl rings, such as **1e** and **1f**, as well as their O-MOM analogues **1i** and **1j** were suitable for this transformation (**4ea**, **4fa**, **4ic**, and **4jk**). The reactions with nucleophiles derived from nonsymmetrical benzoin derivatives were also examined. The benzoin **1g**, bearing a thienyl group, underwent allylation in quantitative yield with an excellent d.r. value of 15:1 and 96 % *ee* (**4ga**). The benzoin analogue **1h**, containing an isobutyl group, reacted with **2a** in a low yield of 38 % and low branched/linear selectivity of 4:1 (5:1 d.r. for the branched product).^[14] However, the identical reaction with the less reactive cinnamyl acetate as the electrophile afforded branched product **4ha** exclusively in high yield (74 %, isolated yield of the major diastereomer) with acceptable diastereoselectivity and excellent enantioselectivity.

Table 2: Iridium-catalyzed allylations of acyclic α -alkoxy ketone enolates: Scope of the allylic carbonates.^[a]

[a] The molar ratio of **1a**/**2**/**3**/LHMDS/CuBr = 2:1:0.02:2:2. The absolute configurations were assigned by analogy. The structure of **4ag** was determined by X-ray analysis. The yields were reported as the combined yields of two diastereoisomers. The diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. The enantiomeric excesses were determined by chiral-phase SFC analysis of major isomers. [b] 0.5 equiv of CuBr was used.

Allylation products containing an O-MOM group on the tertiary alcohol were readily transformed into enantio-enriched tertiary alcohols (**5**) containing adjacent tertiary stereogenic centers (Table 4). Deprotection of **4ba** by reaction with acidic Dowex-50W-X8 resin^[15] (step a) afforded the corresponding alcohols **5ba** in quantitative yield without any erosion of enantiomeric purity. The synthetic value of these allylated benzoin derivatives was further demonstrated by their transformation into highly substituted THF derivatives. Hydroboration of **4ba** with 9-BBN, followed by oxidation

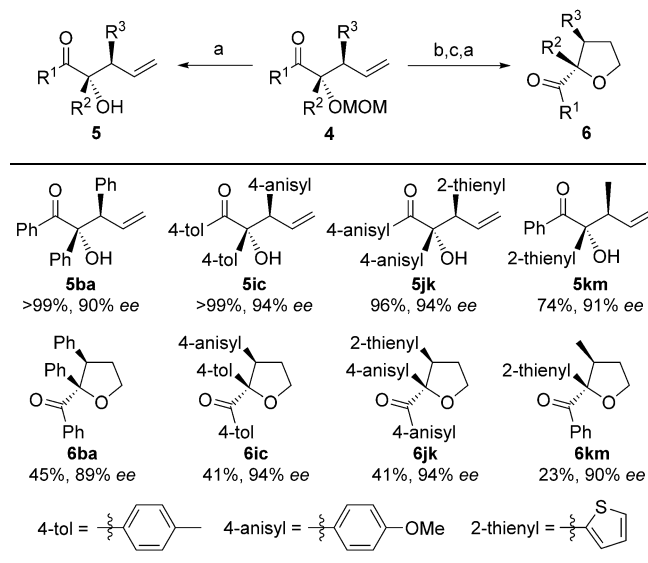
Table 3: Iridium-catalyzed allylation of acyclic α -alkoxy ketone enolates: Scope of ketones.^[a]

[a] The molar ratio of **1**/**2**/**3**/LHMDS/CuBr = 2:1:0.02:2:2. The absolute configurations were assigned by analogy. The yields were reported as the combined yields of two diastereoisomers. The diastereomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. The enantiomeric excesses were determined by chiral-phase SFC analysis of major isomers. [b] 4 mol % of **3** was used. [c] 1 equiv of CuBr was used. [d] 0.5 equiv of CuBr was used. [e] Cinnamyl acetate was used instead of cinnamyl carbonate, and the reaction time was extended to 36 h. The yield reported is that of the isolated major diastereomer.

(step b), yielded the terminal alcohol, which was subsequently converted into the corresponding tosylate (step c). Removal of the MOM protecting group (step a) afforded the free tertiary alcohol, which underwent a 5-*exo-tet* cyclization in situ to furnish the THF derivative **6ba** in 45% yield over three steps.

These synthetic sequences were also applied to the products of allylation bearing different substituents, R^1 , R^2 , and R^3 . In all cases, the substrates **4ic** ($R^1 = R^2 = 4\text{-tol}$, $R^3 = 4\text{-anisyl}$), **4jk** ($R^1 = R^2 = 4\text{-anisyl}$, $R^3 = 2\text{-thienyl}$), and **4km** ($R^1 = \text{Ph}$, $R^2 = 2\text{-thienyl}$ and $R^3 = \text{Me}$) afforded the corresponding tertiary alcohols **5ic**, **5jk**, and **5km** in high yield without erosion of enantiomeric purity. Similarly, the corresponding THF derivatives **6ic**, **6jk**, and **6km** were obtained in high enantiomeric purity.

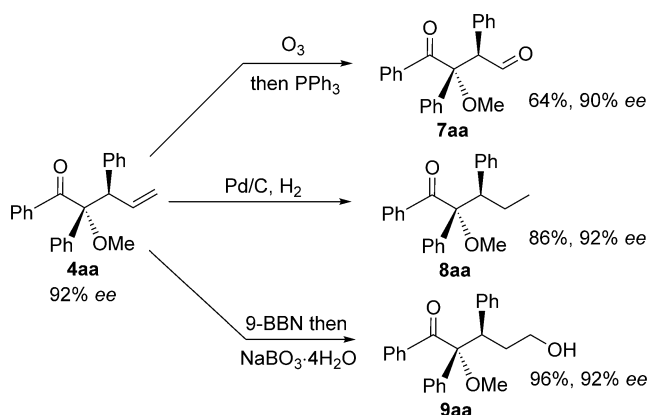
The olefin moiety is a useful precursor to many functional groups. For example, ozonolysis, hydrogenation and the

Table 4: Synthesis of enantioenriched tertiary alcohols (**5**) and tetrahydrofuran derivatives (**6**).^[a]

[a] The yield for **6** is reported as the overall yield of three steps. The absolute structures were assigned by analogy. Steps: a) Dowex-50W-X8 (H⁺ form), MeOH/H₂O (1:1), 65 °C. b) 9-BBN then NaBO₃·4 H₂O. c) TsCl, TEA. 9-BBN = 9-borabicyclo[3.3.1]nonane, TEA = triethylamine, Ts = 4-toluenesulfonyl.

combination of hydroboration and oxidation of the products of allylation **4aa** afforded the aldehyde **7aa**, ketone **8aa**, and primary alcohol **9aa**, respectively, in high yields without erosion of enantiomeric purity (Scheme 2).

In summary, we have developed iridium-catalyzed diastereo- and enantioselective allylic substitutions with unstabilized copper(I) enolates of acyclic α -alkoxy ketones. By employing the metallacyclic complex **3** as the catalyst, LHMDS as the base, and CuBr as the additive, the allylation reactions give products containing vicinal tetrasubstituted and tertiary stereocenters in high yield with excellent d.r. and *ee* values. The geometry of the enolates is controlled by chelation in the presence of a copper(I) cation. The synthetic utility of this method was demonstrated by the synthesis of enantioenriched THF derivatives and tertiary alcohols con-

**Scheme 2.** Derivatizations of **4aa**.

taining adjacent tertiary stereogenic centers. Studies to gain insight into the origin of diastereoselectivity in this reaction are ongoing in our laboratories.

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Keywords: alkylation · asymmetric catalysis · diastereoselectivity · iridium · ketones

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- [9] We also investigated the reactions with a metallacyclic catalyst generated in situ, with the preformed catalysts bearing different ligands, and at different temperatures. The reaction catalyzed by the preformed complex **3** at 5 °C or 0 °C afforded the product in the highest yield and d.r. value. See Table S1 in the Supporting Information for details.
- [10] The solution of copper enolate was heterogeneous and was transferred into the vial containing the allyl carbonate **2** and catalyst **3**. The loss of CuBr was inevitable and not measurable. Considering the low price of CuBr and that an inadequate amount of CuBr would result in lower diastereoselectivity in this reaction (see Table 1, entry 11 versus entry 12), we decided to use excess CuBr (2 equiv) as the additive for further study.
- [11] As observed for the test substrate **2a** (see Table 1, entry 6 vs. entry 12), the reaction of 3,4-dichlorocinnamyl carbonate (**2g**) in the presence of 2 equiv of CuBr gave the product **4ag** in a similar 91 % yield, higher 15:1 d.r., but slightly lower 89 % *ee* than the reaction with 0.5 equiv of CuBr (see the Supporting Information for details), whereas the same reaction with 0.5 equiv of CuBr resulted in similar yield (92 %), slightly lower d.r. (12:1), but excellent *ee* (96 %).
- [12] The reaction of 2-methoxyacetophenone with cinnamyl methyl carbonate afforded the product quantitatively with a d.r. value of 1.9:1. It is possible that the initially formed product underwent epimerization under the reaction conditions to cause the d.r. value of the final product to be low.
- [13] In several cases (**4ca**, **4ea–ga**, **4ic**, **4km**), viscous solutions of copper enolates were observed if 2 equiv of CuBr were added, and the consumption of limiting allylic carbonates was not completed within 12 hours. However, if less CuBr (1 or 0.5 equiv; see the Supporting Information for details) was added, full conversion of the allylic carbonates was obtained within 12 hours.
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