

# Direct and highly regioselective and enantioselective allylation of $\beta$ -diketones

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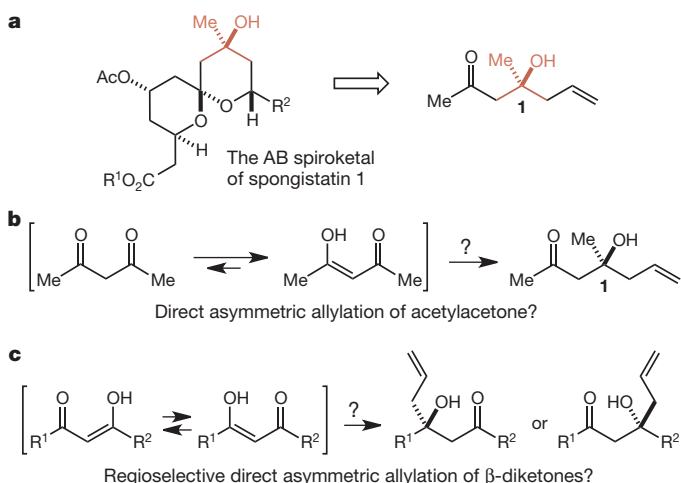
The enantioselective allylation of ketones is a problem of fundamental importance in asymmetric reaction design, especially given that only a very small number of methods can generate tertiary carbinols. Despite the vast amount of attention that synthetic chemists have given to this problem<sup>1–8</sup>, success has generally been limited to just a few simple ketone types. A method for the selective allylation of functionally complex ketones would greatly increase the utility of ketone allylation methods in the chemical synthesis of important targets. Here we describe the operationally simple, direct, regioselective and enantioselective allylation of  $\beta$ -diketones. The strong tendency of  $\beta$ -diketones to act as nucleophilic species was overcome by using their enol form to provide the necessary Brønsted-acid activation. This reaction significantly expands the pool of enantiomerically enriched and functionally complex tertiary carbinols that may be easily accessed. It also overturns more than a century of received wisdom regarding the reactivity of  $\beta$ -diketones.

Chiral non-racemic tertiary carbinols are common in important natural products and in medicinal-chemistry research programmes. Asymmetric ketone allylation is one of the few methods available for their direct synthesis, and over the past 15 years there have been several seminal reports that describe important and significant progress towards the development of efficient, practical and highly enantioselective techniques<sup>1–8</sup>. With only a few exceptions, however, these methods are limited in scope to aryl methyl ketones and aryl linear alkyl ketones (that is,  $\text{ArCOCH}_2\text{R}$ , where Ar is an aryl group and R is hydrogen, an alkyl group or an aryl group). Thus, although efficiency and practicality rightly constitute one major focus in asymmetric reaction design, scope, generality, reliability and applicability in complex settings are equally vital to the realization of methods with truly broad utility and that will be widely adopted<sup>9</sup>.

These thoughts were triggered by our retrosynthesis of the AB spiroketal portion of the potent and precious anti-mitotic marine macrolide spongistatin 1<sup>10–12</sup>—which bears a tertiary carbinol—to  $\beta$ -hydroxyketone **1** (Fig. 1a). It seemed that the ideal<sup>13</sup> synthesis of **1** should involve a direct asymmetric allylation of acetylacetone (Fig. 1b). However, although a few sporadic examples of the non-asymmetric allylation of acetylacetone have been reported<sup>14–16</sup>, there are no known examples of an enantioselective addition of a nucleophile to a  $\beta$ -diketone. In fact, there are simply no general methods that use  $\beta$ -diketones as electrophiles in reactions to form carbon–carbon bonds. This is unsurprising given that  $\beta$ -diketones are not simply compounds with two ketones, but rather are distinct chemical entities that exist primarily in their enol tautomer form. They are rarely used in organic chemical synthesis, and when they are, it is typically as nucleophiles in reactions such as simple alkylations or Knoevenagel condensations. As a result, the synthesis of **1** by means of an asymmetric allylation approach using known methods would require protection or masking of one of the ketones, thus turning what is in principle an ideal synthesis into a multi-step process that would in practice involve protecting-group manipulations and/or oxidation-state adjustments. The development of a method for the direct asymmetric allylation of

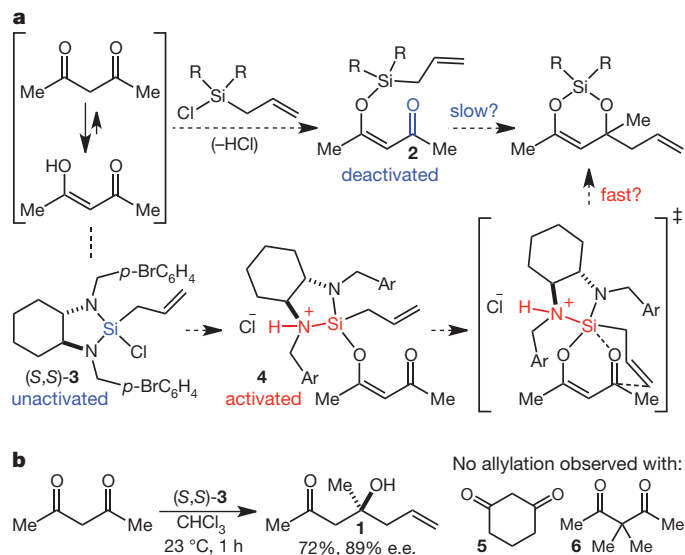
acetylacetone seemed a worthy enough aim, but the ultimate goal of this study became the generalization of such a method to a broad range of  $\beta$ -diketones, including unsymmetrical  $\beta$ -diketones. Far from representing a straightforward extension of the proposed method, however, the allylation of unsymmetrical  $\beta$ -diketones poses a further distinct and formidable challenge: the control of regioselectivity (Fig. 1c). Intrigued by these challenges and by the almost total dearth of useful precedent, we have pursued a general, practical and highly regioselective and enantioselective allylation of  $\beta$ -diketones. We report its successful development and mechanistic elucidation.

Rather than attempting to mask the enol tautomer of the  $\beta$ -diketone *in situ*, preclude its formation or otherwise render it innocuous, our approach centred on the idea that we might instead react it with an allylchlorosilane to generate  $\beta$ -silyloxyenone **2**, which would subsequently undergo intramolecular allylation (Fig. 2a). However, this otherwise beneficial tethering strategy would in this case also lead to deactivation of the ketone electrophile by converting it into a vinylogous silyl ester, raising concerns about whether the desired reaction might be impractically slow and allow competing side reactions (for example, Knoevenagel condensation between **2** and unreacted diketone, or intermolecular diketone allylation by the allylsilane or by **2**). Ideally, then, to favour the desired pathway, the complexation should be very fast, so that no unreacted diketone is available for such side reactions, and the allylsilane should become strongly activated upon complexation. Allylsilane **3** and other related aminosilanes are strongly activated by protonation with Brønsted acids<sup>17,18</sup>. Given that the proposed enol silylation reaction would produce an equivalent of hydrochloric acid, it seemed possible that



**Figure 1 | Origin and evolution of a proposal for a direct, enantioselective and regioselective allylation of  $\beta$ -diketones.** **a**, Retrosynthesis of the AB spiroketal of spongistatin 1 to  $\beta$ -hydroxyketone **1**. Me, methyl group; Ac, acetyl group; R, unspecified group. **b**, A direct asymmetric allylation of acetylacetone would have to contend with the enol form of the diketone. **c**, The generalization of a direct method would require control of regioselectivity.

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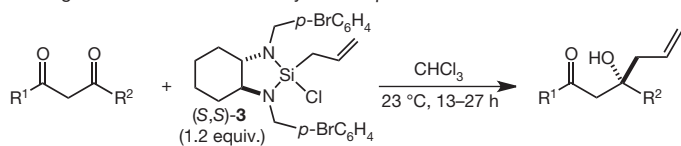


**Figure 2 | Reaction design and proof of concept.** **a**, The reaction design entails tethering the allylsilane to the enol form of the diketone and activation of the silane by the liberated hydrochloric acid (HCl). Ar, aryl group. **b**, First demonstration of the asymmetric allylation of acetylacetone.

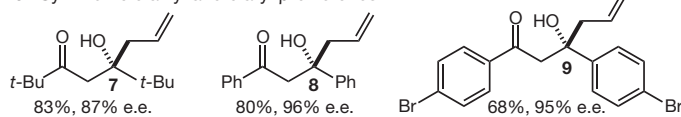
3, which is wholly incapable of allylating ketones, might be perfectly configured to react with  $\beta$ -diketones by way of activated silane complex **4** (Fig. 2a). Indeed, it transpired that allylsilane **3** smoothly allylated acetylacetone, and, on optimization of the reaction conditions ( $\text{CHCl}_3$ , 23 °C, 1 h), produced **1** in 72% yield and 89% enantiomeric excess (e.e.) (Fig. 2b). This operationally simple reaction provides direct and scalable access to **1** from two commercially available compounds, and neither **5** nor **6** was allylated by **3** (Supplementary Fig. 1 and 2), which strongly implies that the underlying mechanistic proposal is sound. The enol form of the diketone, which usually represents a serious functional-group incompatibility, has thus been co-opted as the very functionality responsible for the success of the reaction.

With this proof of concept in hand, we examined the scope of the reaction (Fig. 3a). We began with three further symmetrical  $\beta$ -diketones; as shown (Fig. 3b), products **7**, **8** and **9** were all obtained in good yields and with good to excellent enantioselectivity, establishing that both *t*-butyl and aryl ketones are well tolerated. We next examined a series of unsymmetrical  $\beta$ -diketones, in an effort to establish whether and under what circumstances useful levels of regioselectivity could be realized. Whereas substrates that pitted two alkyl ketones against each other led to little or no regioselectivity, we quickly discovered that substrates that pitted a conjugated ketone against an alkyl ketone consistently reacted such that the allyl group was added to the alkyl ketone with excellent regio- and enantioselectivity (Fig. 3c). This preference not only led to the efficient and selective production of **10–12**, but also operated even when the alkyl group is a *t*-butyl group (as in **13**). Next, we examined 1,3-diphenylpropane-1,3-diones with varying substitutions. We were disappointed at first to find that the *para*-bromo, *para*-methoxy derivative was completely non-selective. When we interrogated the impact of *ortho* substitution, however, subtle effects were revealed (Fig. 3d). Thus, whereas an *ortho*-bromo group regioselectively directs the allylation to the distal ketone (as in **14** and **15**), an *ortho*-methoxy group has the opposite effect (as in **16**) albeit with only moderate (4:1) regioselectivity. These effects are mutually reinforcing, as demonstrated by the reaction of the *ortho*-bromo, *ortho*-methoxy analogue to give **17** as a single regioisomer in 89% yield and 95% e.e., a result that is particularly striking in light of the complete lack of regioselectivity in the reaction of the *para*, *para* isomer. Two final examples (**18** and **19**) show that this *ortho*-effect extends to groups other than bromide, and establish that the methoxy group is the outlier (as in **16**).

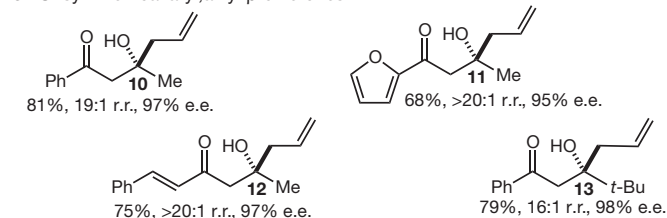
#### a Regio- and enantioselective allylation of $\beta$ -diketones



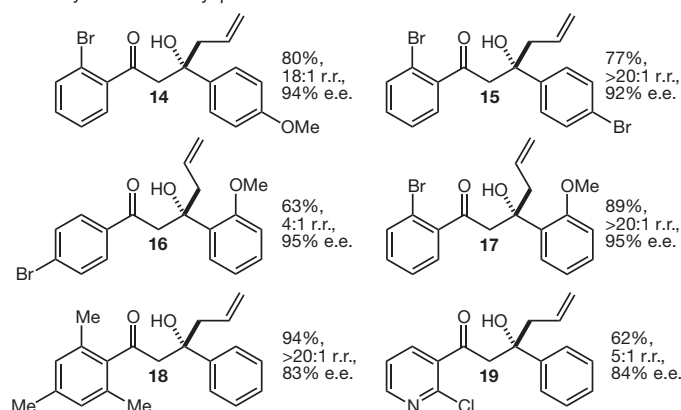
#### b Symmetrical dialkyl and diaryl $\beta$ -diketones



#### c Unsymmetrical aryl, alkyl $\beta$ -diketones

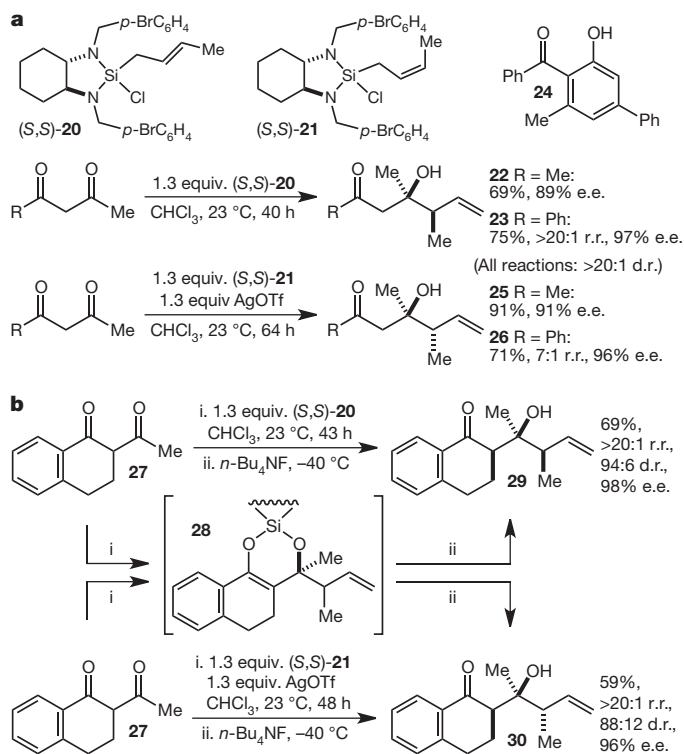


#### d Unsymmetrical diaryl $\beta$ -diketones



**Figure 3 | Scope of the regio- and enantioselective allylation of  $\beta$ -diketones.** **a**, The  $\beta$ -diketone was treated with 1.2 equiv. of (S,S)-**3** in chloroform ( $\text{CHCl}_3$ ) and the resultant mixture was stirred at ambient temperature for 13–27 h. In all cases, the reported yield refers to the yield of isolated (greater than or equal to 20:1 regioisomeric purity) major product after workup and purification by flash chromatography, and the enantiomeric excess (e.e.) was determined by chiral high-performance liquid chromatography. d.r., diastereomer ratio. **b**, Enantioselective allylation of symmetrical  $\beta$ -diketones. Ph, phenyl group. **c**, Regio- and enantioselective allylation of unsymmetrical aryl, alkyl  $\beta$ -diketones (r.r., regioisomer ratio). **d**, Regio- and enantioselective allylation of unsymmetrical diaryl  $\beta$ -diketones.

In principle, the extension of this reaction methodology to crotylation reactions would allow the establishment of a second stereocentre in the allylic position of the homoallylic alcohol products, but examples of highly diastereo- and enantioselective ketone crotylation reactions are rare<sup>5,7,8,19</sup>. We therefore decided to interrogate the ability of crotylsilanes **20** and **21** (ref. 20) to crotylate  $\beta$ -diketones, and found that treatment of acetylacetone and benzoylacetone with *trans*-crotylsilane **20** led to the isolation of **22** (69%, 89% e.e.) and **23** (75%, 97% e.e.) respectively (Fig. 4a). However, treatment of benzoylacetone with *cis*-crotylsilane **21** resulted in a much slower reaction that provided the desired product in very low yield (less than 15%), along with significant amounts of a by-product that we have tentatively identified as **24**. The formation of **24** is readily rationalized as the result of a Knoevenagel condensation cascade that presumably begins with attack of the silyl enol ether complex on unreacted  $\beta$ -diketone. This hypothesis implied that the complexation event is slow in these reactions in general, and that the desired carbon–carbon



**Figure 4** | Regio-, diastereo- and enantioselective crotylation of  $\beta$ -diketones.

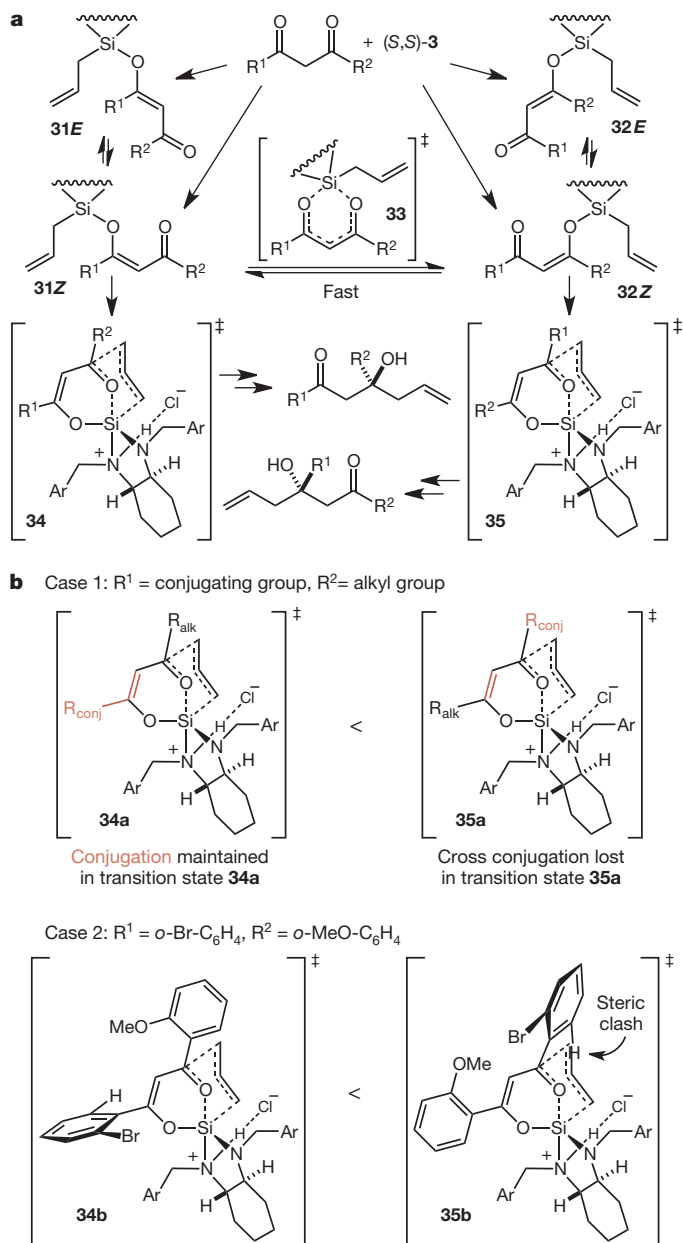
**a**, The crotylation of  $\beta$ -diketones allows the establishment of a second stereocentre in the homoallylic alcohol products. OTf, triflate. **b**,  $\alpha$ -Substitution on the  $\beta$ -diketone substrate may be parlayed into reactions that establish three stereocentres from simple starting materials.

bond-forming step is especially slow in this particular reaction. In this way, the silyl enol ether complex and the starting diketone would both be present in significant concentrations for long periods of time. One way to avoid this could be to accelerate the complexation so that no unreacted diketone would be available to the silyl enol ether complex, and it seemed plausible that replacement of the chloride on the silane with a triflate ( $^-OSO_2CF_3$ ) might accomplish this. Indeed, pretreatment of **21** with  $AgOSO_2CF_3$  before the addition of acetylacetone and benzoylacetone led to vastly improved results, giving **25** and **26** respectively, in excellent yields and enantioselectivities.

Having worked out effective conditions for the crotylation reactions, we next examined 2-acetyltetralone **27** to probe the effect of substitution on the  $\alpha$ -carbon (Fig. 4b). It will be noted that the initial products in these reactions are silyl enol ethers (such as **28**), which are converted to enols that tautomerize to ketones on quench and workup. When the  $\alpha$ -carbon is substituted, as in **28**, the tautomerization has stereochemical consequences, and we have demonstrated in similar systems that good to excellent diastereocontrol may be realized with proper choice of quench/workup conditions<sup>21</sup>. The standard quench for the present method entails cooling the reaction mixtures to  $-40^\circ C$  and adding *n*-Bu<sub>4</sub>NF (where Bu is a butyl group), followed by an aqueous workup. When we quenched and worked up the crotylation reactions of **27** with **20** and **21** using these conditions, good to excellent diastereoselectivity was realized, resulting in the isolation of **29** and **30** in 69% and 59% yield, respectively, with excellent regio- and enantioselectivity. The result is an operationally simple single-step and protecting-group-free synthesis of complex polyketide-like arrays of three stereocentres (including a tertiary carbinol) from simple and readily available starting materials with exceedingly high levels of enantioselectivity.

We next tried to elucidate the mechanistic basis for the remarkable regioselectivity of the reaction. The reaction of an unsymmetrical  $\beta$ -diketone with (*S,S*)-**3** (Fig. 5a) may produce four different

$\beta$ -silyloxyenones (**31E**, **31Z**, **32E** and **32Z**), which may be considered as two regioisomeric pairs of *E* and *Z* isomers. Once it has been established that the *E* and *Z* isomers in each pair interconvert quickly (Supplementary Fig. 3), there are two readily apparent possibilities. The first is that there is no (fast) interconversion between **31Z** and **32Z**, and the regioselectivity is determined by the relative rates of formation of **31** and **32**. The second is that interconversion of **31Z** and **32Z**, presumably by way of **33**, is fast and the regioselectivity is determined by the relative energies of transition states **34** and **35**. To distinguish between these possibilities, we repeated the reaction of **27** with **21** (Fig. 4b) in deuterated chloroform, and monitored it by  $^1H$  NMR spectroscopy (Supplementary Fig. 4). After one hour, the singlet for the methyl group in **27** disappeared and three new singlets appeared at 2.53, 2.11 and 1.97 p.p.m. in a roughly 2:3:4:1 ratio. We have assigned these peaks to the three possible silyl enol ether complexes. Given that the peaks all disappear at the same rate and that this reaction is completely regioselective despite only one of these silyl enol ethers being



**Figure 5** | General mechanism and origin of regioselectivity. **a**, A general mechanistic scheme for the allylation of  $\beta$ -diketones wherein the product distribution is determined by Curtin–Hammett kinetics. **b**, Models for the observed regioselectivity.



able to react directly to give the product, we conclude that in these reactions, the interconversion between **31Z** and **32Z** is fast<sup>22–25</sup> and the regioselectivity is determined by the relative energies of transition states **34** and **35**; that is, the reaction is governed by Curtin–Hammett kinetics<sup>26</sup>.

The regioselectivity observed with substrates wherein  $R^1$  = aryl/alkenyl and  $R^2$  = alkyl (as in Fig. 3c) is difficult to attribute to a simple steric effect, given the regioselective production of **13**. Rather, we propose that the energy of transition state **34a** is lower than that for **35a** because conjugation is maintained in the former pathway but lost completely in the latter (Fig. 5b, case 1). Conversely, we propose that the regioselectivity observed with substrates wherein both  $R^1$  and  $R^2$  are aryl groups and at least one bears *ortho*-substitution (as in Fig. 3d) is the result of steric effects (Fig. 5b, case 2). We expect 2-bromophenyl, mesityl and 2-chloro-3-pyridyl groups to be rotated substantially out of conjugation with the ketones to which they are attached<sup>27–29</sup>, rendering them highly sterically hindered towards nucleophilic attack, as shown in transition state **35b**. By contrast, 2-methoxybenzoyl and *ortho*-unsubstituted phenyl groups are conjugated<sup>30</sup>, allowing an unhindered approach of the allyl group as in transition state **34b**. Thus, in this context, an *ortho*-bromophenyl group is effectively large and an *ortho*-methoxyphenyl group is effectively small. We believe that this steric effect is large enough to overwhelm the complete loss of conjugation in transition state **34b**. The moderate regioselectivity for product **16** is more difficult to rationalize, but it may be that the activation energies for the competing carbon–carbon bond-forming steps are nearly equivalent and the selectivity derives from a modest shifting of the equilibrium constant *K* towards **31Z** owing to the silane's preference for residing away from the larger *ortho*-methoxyphenyl group.

We have demonstrated that it is possible to achieve not only the highly enantioselective allylation and crotylation of  $\beta$ -diketones, but also the highly regioselective allylation and crotylation of unsymmetrical  $\beta$ -diketones. The method allows the protecting-group-free, single-step (that is, ideal) synthesis of functionally and stereochemically complex products from readily available—and undifferentiated— $\beta$ -diketone starting materials. We have elucidated important aspects of the mechanism and found that the regioselectivity is governed by Curtin–Hammett kinetics. This may have important implications for the extension of this methodology to other dicarbonyl substrate types; experiments along these lines are in progress.

## METHODS SUMMARY

The general procedure for the allylation reactions described in Fig. 3 is as follows. To a 0.10 M solution of  $\beta$ -diketone (1.0 equiv.) in anhydrous  $\text{CHCl}_3$  is added (*S,S*)-**3** (1.2 equiv.). The resulting mixture is stirred at ambient temperature (roughly 23 °C) for between 12 and 27 h. The mixture is cooled to –40 °C, *n*-Bu<sub>4</sub>NF (4.0 equiv., 1 M in tetrahydrofuran) is added, and the resulting mixture is maintained at –40 °C for 1 h. Saturated aqueous NH<sub>4</sub>Cl is added and the mixture is allowed to warm to ambient temperature. The mixture is extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers are washed with water and brine, dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue is purified by flash chromatography on silica gel. For complete experimental details and compound characterization, see Supplementary Information.

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Supplementary Information is linked to the online version of the paper at [www.nature.com/nature](http://www.nature.com/nature).

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**Author Contributions** W.A.C. planned and did the vast majority of the experimental work. S.K.R. did the experiments that established the validity of the idea and optimized the allylation of acetylacetone. J.L.L. conceived and directed the project and wrote the manuscript.

**Author Information** X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (<http://www.ccdc.cam.ac.uk/>) under accession code CCDC 874744. Reprints and permissions information is available at [www.nature.com/reprints](http://www.nature.com/reprints). The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at [www.nature.com/nature](http://www.nature.com/nature). Correspondence and requests for materials should be addressed to J.L.L. ([leighton@chem.columbia.edu](mailto:leighton@chem.columbia.edu)).