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Asymmetric Radical Catalysis

Photochemical Organocatalytic Regio- and Enantioselective Conjugate Addition of Allyl Groups to Enals

*Martin Berger, Davide Carboni, and Paolo Melchiorre**

Abstract: *We report the first catalytic enantioselective conjugate addition of allyl groups to α,β-unsaturated aldehydes. The chemistry exploits the visible-light-excitation of chiral iminium ions to activate allyl silanes towards the formation of allylic radicals, which are then intercepted stereoselectively. The underlying radical mechanism of this process overcomes the poor regio- and chemoselectivity that traditionally affects the conjugate allylation of enals proceeding via polar pathways. We also demonstrate how this organocatalytic strategy could selectively install a valuable prenyl fragment at the β-carbon of enals.*

The catalytic asymmetric allylation of carbonyl compounds is a venerable synthetic process that has found wide application for the selective preparation of valuable chiral molecules.[1] In contrast, the *conjugate* allylation of α,β-unsaturated carbonyl substrates has been far less developed. The main difficulty relies on achieving 1,4-selectivity over the inherently preferred 1,2-addition (*chemoselectivity control*, Figure 1 a). Few catalytic methods have been reported that can selectively channel the allylation towards an asymmetric conjugate addition manifold, but they are limited to activated Michael acceptors.[2,3] In addition, only a narrow set of allyl structures, generally restricted to the unsubstituted allyl group, could be installed by these methods.[2] This limitation may arise from the additional complication of competing α- versus γ-addition of the allyl moiety when using substituted allyl reagents (*regioselectivity control*). Despite recent progress,[4] there are still no methods available for the catalytic asymmetric conjugate allylation of α,β-unsaturated aldehydes **1**.

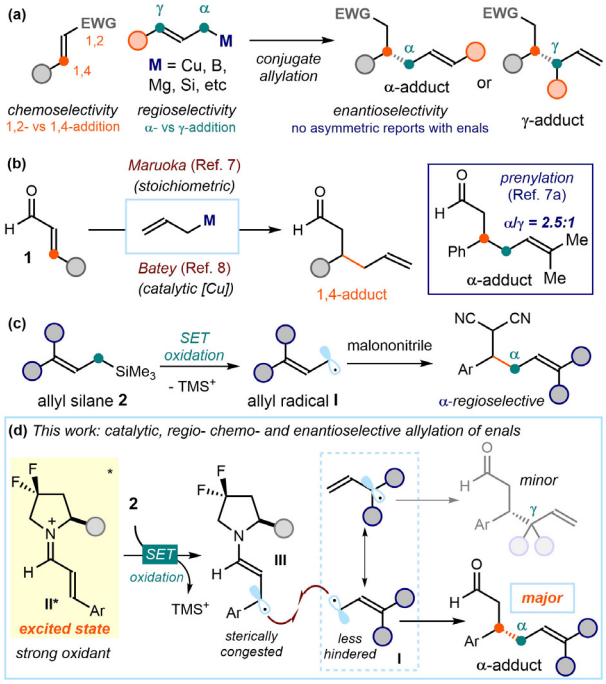

Figure 1. (a) Selectivity challenges connected with conjugate allylation of α,β-unsaturated carbonyl compounds. (b) The two available methods for conjugate allylation of enals **1** are limited to racemic variants. (c) Allylic radicals **I** derived by oxidation of allyl silanes **1** are prone to conjugate addition to activated Michael acceptors with preferred α-regioselectivity. (d) Plan for a catalytic, regio-, chemo-, and enantioselective conjugate allylation of enals **1** based on the excitation of the chiral iminium ion **II**, derived from the activation of **1** with a chiral amine catalyst; single-electron transfer (SET), electron-withdrawing group (EWG), trimethylsilyl (TMS).

Enals are particularly recalcitrant to conjugate allylation chemistry, mainly because of their high tendency to undergo 1,2-addition. Indeed, common strategies, including the use of organocopper reagents[5] or the Hosomi-Sakurai allylation with allylsilanes,[6] are unsuitable to achieve 1,4-chemoselectivity with enals. The only method reported so far for the 1,4-selective allylation required allyllithium reagents under cryogenic conditions in the presence of stoichiometric amounts of a bulky fluorinated aluminum-based Lewis acid (Figure 1 b).[7] Interestingly, the steric profile of the Lewis acid allowed the installation of a synthetically valuable prenyl group at the β-carbon of cinnamaldehyde with moderate α-regioselectivity.[7a] Recently, a copper-based catalytic protocol was developed that accounts for the chemoselective conjugate addition of the plain allyl group to enals.[8] However, the use of substituted allyl moieties was not tolerated. To date, the asymmetric conjugate allylation of α,β-unsaturated aldehydes

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has remained an unconquered target, even in a stoichiometric regime. Herein, we report an initial solution to this problem, detailing the first catalytic asymmetric method for the conjugate addition of allyl groups to aromatic enals proceeding with high chemo- and α-regioselectivity and moderate enantiocontrol.

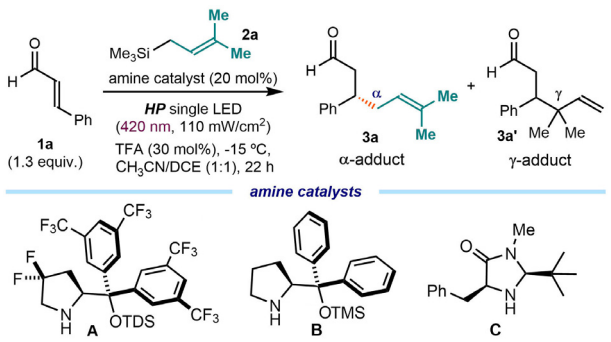
Our design plan was informed by the notion that classical ionic pathways are not suitable for the conjugate allylation of enals.[5,6] We therefore considered using a completely different reactivity, based on radical mechanisms, to achieve this target. This idea finds support in previous studies demonstrating that allyl silanes **2**, which are not suitable nucleophiles for 1,4-addition to enals via polar manifolds,[6] can be readily oxidized to generate an allyl radical **I**[9] upon fragmentation of the silicon redox-auxiliary group.[10] Radical **I** has a proven propensity to attack activated Michael acceptors (e.g. benzylidene malononitrile) with α-regioselectivity (Figure 1c).[11] We surmised that the reactivity of allylic radicals could be further leveraged to develop a conjugate addition to less activated enals **1**. To implement this idea in an enantioselective setting, we exploited our recently reported strategy based on the photoexcitation of chiral iminium ions **II**,[12] generated upon condensation of a chiral amine catalyst with enals **1** (Figure 1d). The excited intermediate **II*** is a strong oxidant, which can generate radicals upon single-electron transfer (SET) activation of easy-to-oxidize substrates, including organic silanes.[12a] If this photochemical SET mechanism could be used to activate allyl silanes **2** too, then an allylic radical **I** would be generated. A stereocontrolled radical coupling between **I** and the chiral 5π-electron β-enaminyl radical intermediate **III**, ensuing from the SET event, would eventually afford the chiral allylation product. Considering the steric profile of the intermediate **III** and the tendency of **I** to attack Michael acceptors with α-selectivity,[11] we envisaged that this strategy could provide a solution to the long-standing problem of achieving stereo-, regio-, and chemoselectivity in the conjugate allylation of enals **1**.

To test the feasibility of our plan, we selected cinnamaldehyde **1a** and the *gem*-difluorinated diarylprolinol silylether catalyst **A**[12a] for the formation of the chiral iminium ion **II** (Table 1). The experiments were conducted in an acetonitrile/1,2-dichloroethane (CH_3CN/DCE) mixture using a single high-power (HP) LED (λ_{max} = 420 nm) with an irradiance at 110 mW cm^{-2} (details of the illumination set-up are reported in the Supporting Information, Figure S5). We selected the prenyl silane **2a** as the radical precursor for two reasons: *i*) firstly, **2a** has an electrochemical potential (E^{ox} (**2a**$^{\cdot+}$/**2a**) = +1.7 V vs. Ag/AgCl in CH_3CN; see cyclic voltammetry studies in the Supporting Information) that falls within the oxidation range of the excited iminium ion **II*** (estimated E^* (**II***/**II**$^{-}$) ≈ +2.4 V vs. Ag/Ag$^+$ in CH_3CN);[12a] *ii*) secondly, this would allow to stereoselectively install the valuable prenyl group at the β-carbon of enals (product **3a**). Given the wide occurrence of the prenyl fragment in natural products and biologically important molecules,[13] direct methods for its installation are highly sought-after,[13c–e] but few asymmetric catalytic variants are available.[14]

After extensive optimization and performing the reaction at −15 °C using a slight excess of cinnamaldehyde **1a** (1.3 equiv), we obtained the desired prenylation product **3a** in synthetically useful yield and enantiomeric ratio (50% yield, 83:17 er, entry 1). Importantly, the reaction proceeded with high α-regioselectivity, preferentially leading to the linear prenylated product **3a** (90:10 regioisomeric ratio, rr). Performing the reaction with a larger excess of **1a** or at ambient temperature severely affected both reactivity and regioselectivity (entries 2 and 3). A control experiment indicated that light is required for reactivity (entry 4), suggesting that a photocatalytic radical pathway, and not an ionic background process, is responsible for the formation of both the linear (**3a**) and branched (**3a′**) allylation products. No product was formed without catalyst **A** (entry 5), while other chiral amine catalysts **B** and **C** led to a complete loss of reactivity or unsatisfactory results, respectively (entries 6 and 7). The addition of water (entry 8) or the use of acids other than TFA, including CCl_3CO_2H (entry 9) or $MeSO_3H$ (entry 10), significantly affected the efficiency of the system.

Using the optimized conditions described in Table 1, entry 1, we then explored the selective installation of structurally more demanding allyl moieties onto cinnamaldehyde **1a** (Figure 2a). A cyclic allyl silane afforded product **3b** with high α-regioselectivity, while the ether-containing substrate provided product **3c** as a single regioisomer. Increasing the steric hindrance of the allyl precursor secured the exclusive formation of the linear isomers (products **3d** and **3e**), albeit at the expense of reactivity for **3e**. Non-symmetri-

Table 1: Optimization studies and control experiments.[a]



Entry	Deviation	Amine	Yield[b] [%]	rr [%]	er[c] [%]
1	none	**A**	50[d]	90:10	83:17
2	3 equiv of **1a**	**A**	17	80:20	83:17
3	room temperature	**A**	14	56:44	74:26
4	no light	**A**	0	–	–
5	no catalyst	–	0	–	–
6	none	**B**	0	–	–
7	none	**C**	31	72:28	62:38
8	with 10 equiv. water	**A**	30[e]	71:29[e]	n.d.
9	with CCl_3CO_2H	**A**	20[e]	70:30[e]	n.d.
10	with $MeSO_3H$	**A**	0	–	–

[a] Reaction performed on a 0.1 mmol scale for 22 h at −15 °C using solvent (0.2 mL) under illumination by a single high-power (HP) LED (λ_{max} = 420 nm) with an irradiance of 110 mW cm^{-2}. [b] Yields of a mixture of isolated α-adduct (**3a**) and γ-adduct (**3a′**). [c] Enantiomeric ratio of the major regioisomer **3a**. [d] Average of three runs. [e] Yield determined by ^{1}H NMR analysis of the crude mixture. Key: trifluoroacetic acid (TFA), trimethylsilyl (TMS), thexyldimethylsilyl (TDS), not determined (n.d.).

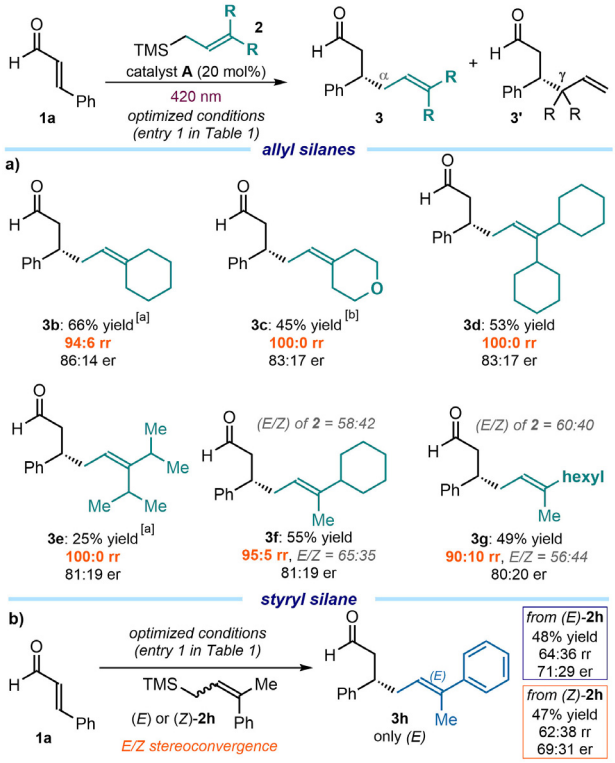


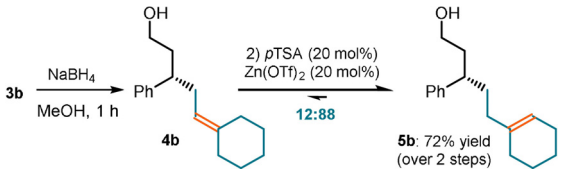
Figure 2. Substrate scope for the conjugate allylation of cinnamaldehyde **1a**. Survey of the (a) aliphatic and (b) aromatic allylic silanes that can participate in the reaction. Reactions performed on a 0.1 mmol scale using 1.3 equiv of **1a** at −15 °C in 0.2 mL of a CH_3CN/DCE mixture under illumination by a single HP LED (λ_{max} = 420 nm) with an irradiance of 110 mW cm^{-2}. Yields and selectivity of the isolated products **3** are reported below each entry (average of two runs per substrate). [a] Average of three runs. [b] Performed in CH_3CN.

cally disubstituted allylic silanes led to the formation of **3f** and **3g** with high regioselectivity.

Interestingly, the geometrical composition of the silane substrates, which were used as inseparable (*E*/*Z*)-mixtures, directly translated into products **3f** and **3g**, which were obtained as a mixture of double bond isomers with similar (*E*/*Z*) ratio. This is in contrast to the stereoconvergent pathway observed when using a non-symmetrical styryl silane (Figure 2b), which afforded exclusively the *(E)*-isomer of product **3h** starting from either geometrically pure *(E)*- or *(Z)*-substrates **2h**. Since the silane substrate *(Z)*-**2h** is configurationally stable under the reaction conditions, we propose that a rapid isomerization[15] of the styryl radical is at play. This complete *E* selectivity in **3h** came along with a slightly decreased regio- and enantioselectivity. As a limitation of the system, allyltrimethylsilane and methallylsilane failed to provide useful results (a list of unsuccessful substrates is reported in Figure S1). Further experiments revealed that methallylsilane is rapidly consumed by protodesilylation under the reaction conditions.

We then investigated the scope of α,β-unsaturated aldehydes **1** using the cyclic silane **2b** (E^{ox} (**2b**$^{\cdot+}$/**2b**) ≈ + 1.4 V vs. Ag/AgCl in CH_3CN) as the allyl radical precursor (Figure 3a). A high degree of regioselectivity was consistently observed, the α-adduct being formed preferentially (rr mostly ranging from 90:10 to 99:1). Both electron-withdrawing (products **3i-m**) and electron-donating groups (**3n-q**) on the aromatic ring are well tolerated without diminishing the yield or enantioselectivity. The substituent can also be moved around the ring without impeding reactivity (**3o-q**). Notably, synthetically useful groups, which can undergo further functionalization, were tolerated, including halogens (**3k–m**) and trimethylsilyl (**3r**). One limitation of the system is that aliphatic enals, including (*E*)-2-octenal or 4,4-dimethyl-2-pentenal, remained unreacted when irradiated under 365 nm (for further details see the Supporting Information, Section 3). The absolute configuration of the products was unambiguously assigned by X-ray crystallographic analysis of **3i**.[16] Finally, given the synthetic utility of an asymmetric catalytic prenylation method, we demonstrated that other enals are suitable for the selective conjugate installation of the prenyl group using silane **2a** (products **3s–u**, Figure 3b).

Although isomerization of alkenes may occur under acidic conditions, we did not observe any migration of the double bond in products **3**, which are stable under our conditions. Since olefin isomerization is an attractive approach to achieve rapid diversification,[17] we demonstrated for product **3b** that migration from the exocyclic to the endocyclic position is feasible (Scheme 1). Upon reduction of **3b** and exposure of alcohol **4b** to acidic conditions, a clean migration process leading to the endocyclic alkene **5b** was observed.



Scheme 1. Reduction/isomerization sequence of **3b** yielding alcohol **5b** (in equilibrium with precursor **4b**, 88:12 ratio); **5b** was isolated with 84% purity with small amounts of inseparable starting alcohol; *para*-toluenesulfonic acid (*p*TSA).

Mechanistically, we believe that this transformation is triggered by the excitation of the iminium ion **II**, as depicted in Scheme 2. The ensuing SET oxidation of the allyl silane **2** concomitantly forms the chiral 5π-intermediate **III** and a radical cation **IV**, which undergoes rapid solvent-assisted desilylation to afford the allylic radical **I**.[18] A stereocontrolled radical coupling[19] then affords the allylation product **3** with high chemo- and α-regioselectivity and good enantiocontrol. We also considered a mechanism based on a radical chain propagation, which would require the allyl radical **I** to add to the ground-state iminium ion **II**. This path is not congruent with the low quantum (ϕ) measured for the formation of product **3c**, which was found to be as low as 0.01 (for details on the use of potassium ferrioxalate as an actinometer, see the Supporting Information).

In summary, we reported the first catalytic system suitable for the enantioselective conjugate addition of allyl groups to enals. The process exploits a photoinduced radical process orchestrated by the excitation of chiral iminium ions. The method offers complete chemoselectivity, high α-regioselec-

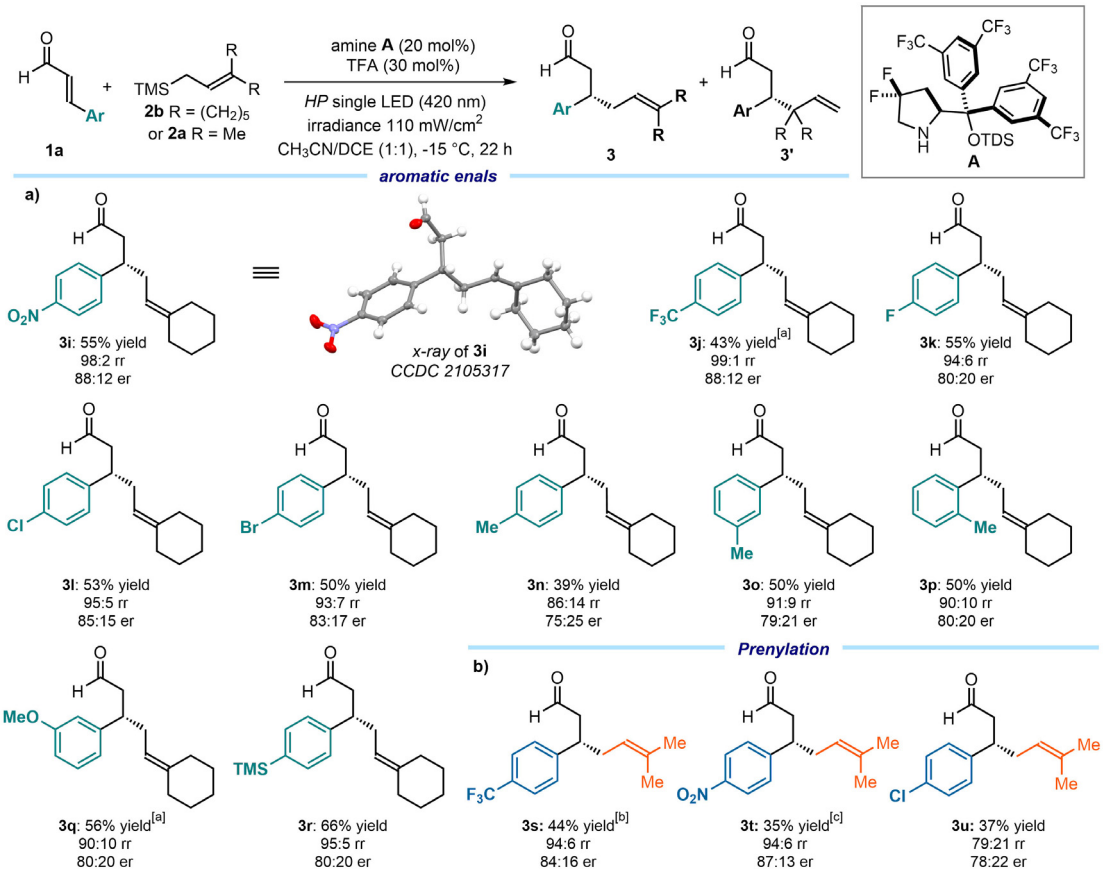
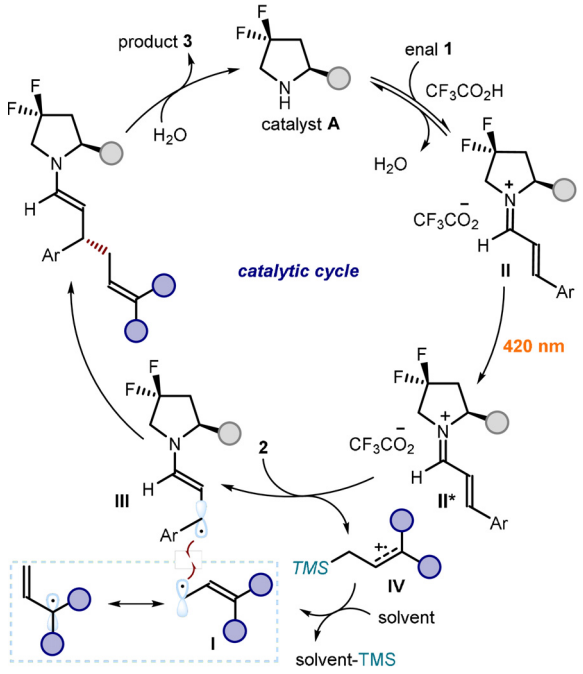


Figure 3. (a) Scope of the regio- and enantioselective conjugate allylation of aromatic enals using silane **2b**. (b) Catalytic asymmetric prenylation of enals using prenyl silane **2a**; yields and selectivity of the isolated products **3** are reported below each entry (average of two runs per substrate). [a] Reaction time: 48 h. [b] Reaction time: 96 h. [c] Reaction time: 62 h.



Scheme 2. Proposed mechanism.

tivity, moderate to good enantioselectivity and yields, and it is useful for the stereoselective prenylation of enals. We hope this report may ignite further efforts to broaden the utility of the enantioselective conjugate allylation of enals, which has remained an elusive reaction so far.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: allylation · enantioselectivity · organocatalysis · photochemistry · regioselectivity

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