Asymmetric Catalysis

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# Asymmetric γ-Allylation of α,β-Unsaturated Aldehydes by Combined Organocatalysis and Transition-Metal Catalysis**

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***Abstract:*** *The first asymmetric regio- and diastereodivergent γ-allylation of cyclic α,β-unsaturated aldehydes based on combined organocatalysis and transition-metal catalysis is disclosed. By combining an aminocatalyst with an iridium catalyst, both diastereomers of branched allylated products can be achieved in moderate to good yields and excellent regio- and stereoselectivities. Furthermore, by replacing the iridium catalyst with a palladium catalyst, the linear allylated products are formed in good yields and excellent regio- and enantioselectivities. The developed method thus provides selective access to all six isomers of the γ-allylated product in a divergent fashion by choosing the appropriate combination of organocatalyst, transition-metal catalyst, and ligand.*

The ability to perform reactions in a selective and predictable manner is a cornerstone of synthetic organic chemistry. In the last decades, catalysis has been established as the state-of-the-art method for performing reactions in an efficient and selective manner.[1] Even though the development of catalytic approaches has allowed tremendous progress in the ability to form products in a selective fashion, the ability to access the full array of isomers in a divergent fashion remains a challenge. For transition-metal-catalyzed allylic alkylation of nucleophiles, a reaction which represents one of the fundamental carbon–carbon and carbon–heteroatom bond-forming reactions (Figure 1 a), the most important selectivity issues are the control of regio- and stereoselectivity. In the last decades, remarkable progress has been made in the area of stereoselective allylations of nucleophiles and a large number of asymmetric versions have been disclosed.[2] Traditionally, stereoinduction is achieved by applying chiral ligands in combination with a metal catalyst. With respect to the regioselectivity of allylation reactions, access to a variety of both linear and branched products has been achieved, although the selectivity is often dependent on the applied substrates and reaction conditions. Achieving selective access to both regioisomers of the products in a divergent fashion is thus no simple task and typically two different methodologies must be developed.[3]

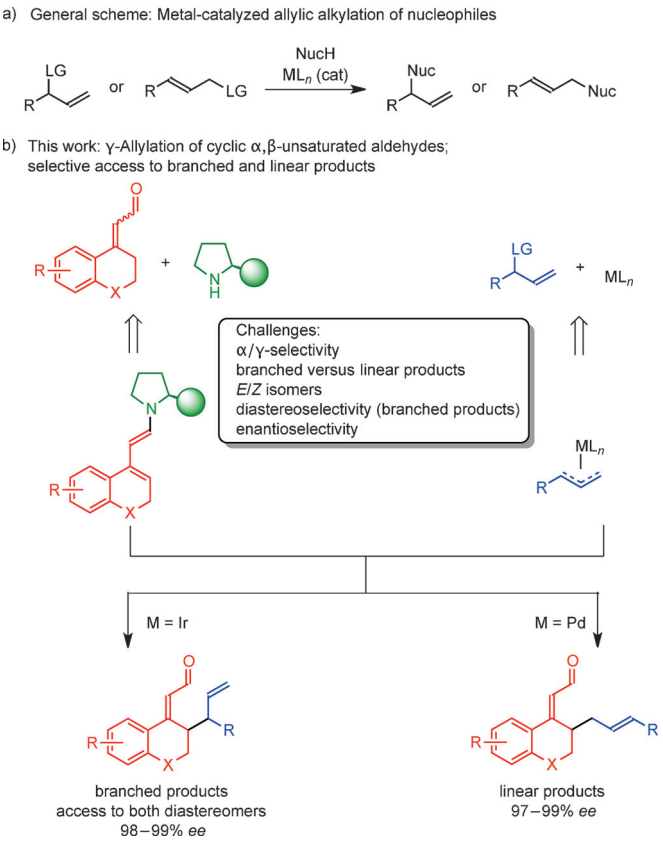


***Figure 1.*** General allylic alkylation of nucleophiles and asymmetric regio- and diastereodivergent γ-allylation of cyclic α,β-unsaturated aldehydes.

In the last 15 years, organocatalysis has been established as the third pillar in asymmetric catalysis.[4] A remarkable feature of this mode of catalysis is the ability of aminocatalysts to promote asymmetric reactions by both HOMO-raising and LUMO-lowering strategies. In recent years, two new exciting fields have emerged in organocatalysis: firstly, the application of vinylogous aminocatalysis has proven successful in asymmetric functionalization at remote centers of polyunsaturated carbonyl compounds.[5] Secondly, the combination of organocatalysis with metal catalysis represents another exciting development which has proven useful for otherwise elusive asymmetric reactions.[6] Despite the promise of these two branches of organocatalysis, the combination of vinylogous aminocatalysis with transition-metal catalysis in individual catalytic cycles is rare.[7]

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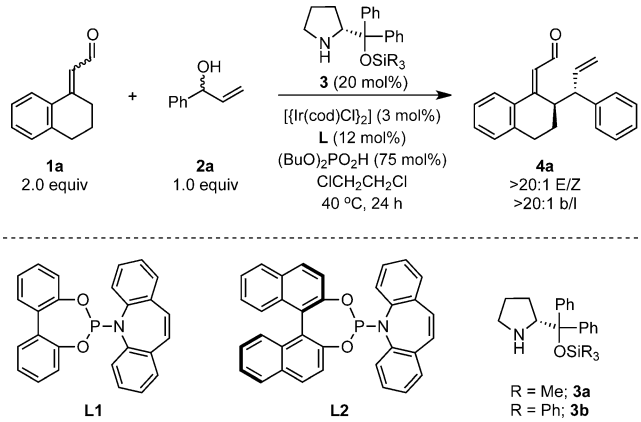
The α-allylation of carbonyl compounds is an efficient methodology for the formation of carbon–carbon bonds.[8] Previously, preactivated carbonyl compounds have been employed.[9] The requirement to prefunctionalize the carbonyl compound reduces the overall atom economy of the process and therefore represents a drawback in these methods. Significant progress has been achieved in this area by the development of catalytic versions based on combined organocatalysis and metal catalysis.[10] In these systems the nucleophilic carbonyl compound is activated by an organocatalyst, whereas the electrophilic π-allyl system is formed by activation with a transition metal in two separate catalytic cycles. The preactivation of the carbonyl compound can thus be circumvented.

Inspired by the recent advances in α-allylation of carbonyl compounds as well as vinylogous aminocatalysis, we set out to explore an asymmetric γ-allylation of cyclic α,β-unsaturated aldehydes based on combined organocatalysis and transition-metal catalysis (Figure 1b).[11,12] The envisioned transformation is associated with several potential selectivity issues. The reactive dienamine intermediate contains two nucleophilic sites, hence the regioselectivity (α- versus γ-allylation) of the α,β-unsaturated aldehyde poses a challenge. Likewise, the activated π-allyl system has two electrophilic sites and the regioselectivity (branched versus linear products) of this intermediate also needs to be controlled. Furthermore, the control of the *E/Z* ratio, the diastereomeric ratio (for branched products), and enantiomeric excess of the products may be problematic.

In the following, we disclose the first asymmetric and highly selective regio- and diastereodivergent γ-allylation of cyclic α,β-unsaturated aldehydes. By the employment of a diphenylprolinol silyl ether catalyst[13] in combination with an iridium catalyst, selective access to branched γ-allylated products can be achieved in excellent diastereo- and enantioselectivity. This approach is based on stereodivergent dual catalysis,[10g–i] and thus allows selective access to both diastereomers of the branched products through the combination of two distinct chiral catalytic systems. Furthermore, it is shown that the linear products of the γ-allylation can be formed in excellent enantioselectivity by replacing the iridium catalyst with a palladium catalyst under otherwise similar reaction conditions. The developed method thus provides access to all six isomers of the γ-allylated product (4 stereoisomers of branched product, 2 enantiomers of linear product) in a divergent fashion, in greater than 95% selectivity, by choosing the appropriate combination of aminocatalyst, transition-metal catalyst, and ligand.

Initially our focus turned towards developing a method allowing the selective access to the branched products. Recent reports on iridium-catalyzed allylations have shown this type of catalysis to be a widely applicable method for the formation of branched products in high enantioselectivity.[14] Furthermore, the recent work by Carreira and co-workers demonstrated that iridium-catalyzed allylations are compatible with aminocatalysis,[10g–i] thus an iridium-based catalyst was a promising candidate for activation of the π-allyl system for this transformation. A promising starting point for the optimization of the reaction was achieved when the cyclic α,β-unsaturated aldehyde **1a** was employed with the allylic alcohol **2a**, 20 mol% of the aminocatalyst **3a**, carrying a TMS-protecting group, 3 mol% of the [{Ir(cod)Cl}$_2$] catalyst, 12 mol% of the achiral phosphoramidite ligand **L1**, and 75 mol% of $(BuO_2)PO_2H$ as a promoter in 1,2-dichloroethane at 40°C (Table 1). The γ-allylated product **4a** was obtained in high enantioselectivity. However, significant amounts of the α-allylated product as well as a poor control of diastereoselectivity were observed (entry 1). These reaction conditions gave significant amounts of the aldol condensation product along with other unidentified side products. By changing the ligand to **L2**, a significant increase in the diastereoselectivity was achieved, as well as an improved control of the γ- versus α-product ratio, and the desired product was isolated in near perfect enantioselectivity (entry 2). The observation that increased bulk in the catalytic system could improve the selectivity of the reaction spurred us to test the reaction using the aminocatalyst **3b**, which carries a bulky triphenyl-protecting group. When this catalyst was combined with **L1**, an improvement in γ- versus α-selectivity was observed (entry 3) as compared to that obtained when **3a** was used (entry 1). Satisfyingly, by

***Table 1:*** Optimization of the asymmetric γ-allylation of **1a** by dual catalysis.[a]



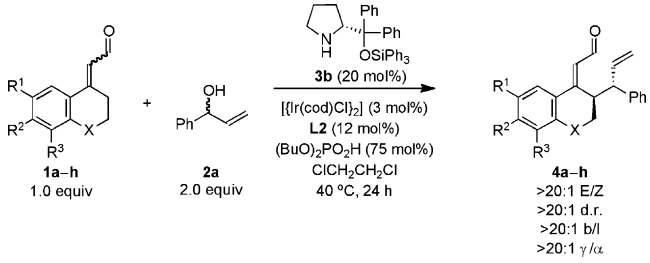

| Entry | L | Conv. [%][b] | γ/α[c] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1[e,g] | **L1** | 87 | 1.3:1 | 1.4:1 | 92 |
| 2[e,g] | **L2** | 57 | 6.8:1 | >20:1 | 99 |
| 3[f,g] | **L1** | 65 | 4.8:1 | 1.6:1 | 97 |
| 4[f] | **L2** | 55 | >20:1 | >20:1 | 99 |
| 5[f,h] | **L2** | 19 | – | – | – |
| 6[f,i] | **L2** | <5 | – | – | – |
| 7[f,j] | **L2** | 95 (66) | >20:1 | >20:1 | 99 |

[a] See the Supporting Information for experimental details. [b] Conversion of limiting reagent as determined by $^1$H NMR analysis of the crude reaction mixture. Yield of isolated **4a** is shown within parentheses. [c] Determined by $^1$H NMR analysis of the crude reaction mixture of **4a**. [d] Determined by UPC$^2$ using a chiral stationary phase. [e] The catalyst **3a** was employed. [f] The catalyst **3b** was employed. [g] A messy reaction with aldol condensation and unidentified side products was observed by $^1$H NMR analysis of the crude reaction mixture. [h] 50 mol% $CF_3CO_2H$ was employed instead of $(BuO)_2PO_2H$. [i] 5 mol% $Zn(OTf)_2$ was employed instead of $(BuO)_2PO_2H$. [j] 1.0 equiv of **1a** and 2.0 equiv of **2a** was employed.

combining **3b** and **L2**, a clean reaction was achieved, thus affording a single isomer of the product (entry 4), although only 55% conversion of **2a** was obtained within 24 hours. In an attempt to improve the conversion, other promoters were tested in the reaction. However, the employment of TFA (entry 5) and $Zn(OTf)_2$ (entry 6) afforded only minor conversion. Ultimately, it was found that reversing the stoichiometry of the reactants provided almost full conversion and the intended product **4a** could be isolated in 66% yield (entry 7).[15] It should be noted that in all experiments exclusive formation of the branched product and *E* isomer of aldehyde was observed.

With the optimal reaction conditions in hand we moved on to explore the scope of the reaction by initially focusing on the aldehyde (Table 2). α,β-Unsaturated aldehydes bearing no substituents (**1a**), as well as those with electron-rich (**1b–d**) and electron-deficient substituents (**1e**) in various positions on the aromatic moiety, all performed well in the reaction, thus yielding their respective products (**4a–e**) in modest to good yields and excellent regio- and stereoselectivities (entries 1–5). It was found, however, that the employment of the α,β-unsaturated aldehyde **1c** resulted in prolonged reaction times and a slightly diminished yield (entry 3). This outcome is possibly due to the ability of the methoxy-substituent to conjugate a lone pair of electrons into the unsaturated aldehyde moiety, thus retarding condensation with the catalyst. A disubstituted α,β-unsaturated aldehyde (**1f**) also performed well in the reaction (entry 6). Furthermore, α,β-unsaturated aldehydes containing a heteroatom in the nonaromatic cycle (**1g**,**h**) were successfully employed, thus affording the desired products (**4g**,**h**) in good yields and excellent selectivities (entries 7 and 8). We have also tested related linear systems, but unfortunately these substrates give a mixture of products and are less reactive than those given in Table 2.

***Table 2:*** Scope of the asymmetric γ-allylation with respect to the aldehydes **1** to form branched products.[a]

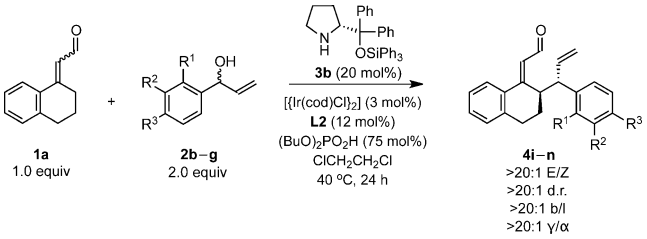



| Entry | $R^1$, $R^2$, $R^3$, X | Yield [%] | *ee* [%][b] |
|---|---|---|---|
| 1 | H, H, H, $CH_2$ (**1a**) | **4a**: 66 | 99 |
| 2[c,d] | MeO, H, H, $CH_2$ (**1b**) | **4b**: 64 | 98 |
| 3[c,e] | H, MeO, H, $CH_2$ (**1c**) | **4c**: 40 | 98 |
| 4 | H, H, MeO, $CH_2$ (**1d**) | **4d**: 56 | >99 |
| 5 | F, H, H, $CH_2$ (**1e**) | **4e**: 61 | >99 |
| 6 | Me, H, Me, $CH_2$ (**1f**) | **4f**: 68 | 99 |
| 7[c] | H, H, H, O (**1g**) | **4g**: 74 | >99 |
| 8[c,f] | H, H, H, S (**1h**) | **4h**: 64 | >99 |

[a] Reactions were performed on a 0.1 mmol scale. Absolute configuration was determined by X-ray crystallography analysis of a derivative of **4a** and the remaining structures were assigned by analogy (see the Supporting Information for details). [b] Determined by UPC$^2$ using a chiral stationary phase. [c] Aldehyde was functionalized by in situ Wittig olefination prior to isolation. [d] A 94:6 d.r. was observed. [e] The reaction was performed for 72 h. [f] A 90:10 d.r. was observed.

Subsequently, the scope with respect to the allylic alcohol was explored (Table 3). Methyl substitution was tolerated in both the *ortho*-, *meta*-, and *para*-positions of the allylic alcohol (**2b–d**), thus providing the corresponding products (**4i–k**) in good yields and excellent regio- and stereoselectivities (entries 1–3). Additionally, allylic alcohols with electron-rich (**2e**) and electron-deficient substituents (**2f**,**g**) provided similar results (entries 4–6).

***Table 3:*** Scope with respect to the allylic alcohol in the asymmetric γ-allylation **1a** to form branched products.[a]




| Entry | $R^1$, $R^2$, $R^3$ | Yield [%] | *ee* [%][b] |
|---|---|---|---|
| 1 | Me, H, H (**2b**) | **4i**: 64 | >99 |
| 2 | H, Me, H (**2c**) | **4j**: 70 | 99 |
| 3 | H, H, Me (**2d**) | **4k**: 61 | >99 |
| 4 | H, H, MeO (**2e**) | **4l**: 71 | >99 |
| 5 | H, H, Br (**2f**) | **4m**: 63 | >99 |
| 6 | H, H, $NO_2$ (**2g**) | **4n**: 65 | >99 |

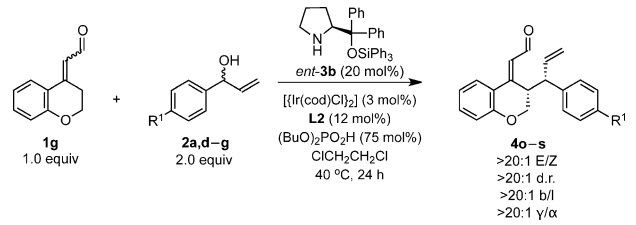
[a] Reactions were performed on a 0.1 mmol scale. See the Supporting Information for experimental details. [b] Determined by UPC$^2$ using a chiral stationary phase.

Given the well-documented ability to access all stereoisomers of allylated products in a divergent fashion by combined amino and iridium catalysis,[10g–i] we decided to test whether the opposite diastereoisomer of the branched product **4** could be accessed by simply employing the enantiomer of the catalyst *ent*-**3b** (Table 4). Gratifyingly, it was found that employing the α,β-unsaturated aldehyde **1g** under these reaction conditions furnished the product **4o** (the diastereomer of **4g**) in decent yield and excellent diastereo- and enantioselectivity (entry 1). Various *para*-substituted allylic alcohols (**2d–g**) were used in the reaction and gave their corresponding products (**4p–s**) in decent to good yields and excellent stereoselectivities (entries 2–5).

At this point, we set out to develop a method for the formation of linear γ-allylated products. It was envisioned that the regioselectivity could be controlled by exchanging the metal species, and given the propensity of palladium-based catalysts to promote the desired regioselectivity,[2,16] our focus turned towards these type of catalysts. To our delight, employment of a palladium catalyst under otherwise similar reaction conditions (see the Supporting Information for optimization) facilitated the formation of linear products (**6**) in excellent selectivity (Table 5). The scope of the reaction

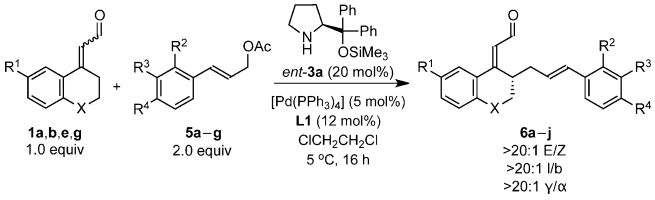
***Table 4:*** Scope with respect to the allylic alcohol in the asymmetric γ-allylation **1g** to form the opposite diastereomer of the branched products **4**.[a]




| Entry | $R^1$ | Yield [%] | *ee* [%][b] |
|---|---|---|---|
| 1 | H (**2a**) | **4o**: 52 | >99 |
| 2 | Me (**2d**) | **4p**: 62 | >99 |
| 3 | MeO (**2e**) | **4q**: 78 | >99 |
| 4[c] | Br (**2f**) | **4r**: 51 | 98 |
| 5[d] | $NO_2$ (**2g**) | **4s**: 54 | 99 |

[a] Reactions were performed on a 0.1 mmol scale. See the Supporting Information for experimental details. [b] Determined by UPC$^2$ using a chiral stationary phase. [c] 72 h reaction time. [d] 96 h reaction time.

***Table 5:*** Scope of the asymmetric γ-allylation with respect to the aldehydes **1** to form the linear products **6**.[a]




| Entry | $R^1$, X | $R^2$, $R^3$, $R^4$ | Yield [%] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | H, $CH_2$ (**1a**) | H, H, H (**5a**) | **6a**: 75 | 98 |
| 2 | MeO, $CH_2$ (**1b**) | H, H, H (**5a**) | **6b**: 68 | 98 |
| 3 | F, $CH_2$ (**1e**) | H, H, H (**5a**) | **6c**: 64 | >99 |
| 4 | H, O (**1g**) | H, H, H (**5a**) | **6d**: 70 | 97 |
| 5 | H, $CH_2$ (**1a**) | Me, H, H (**5b**) | **6e**: 76 | 98 |
| 6 | H, $CH_2$ (**1a**) | H, Me, H (**5c**) | **6f**: 74 | 99 |
| 7 | H, $CH_2$ (**1a**) | H, H, Me (**5d**) | **6g**: 72 | 98 |
| 8 | H, $CH_2$ (**1a**) | H, H, MeO (**5e**) | **6h**: 75 | 99 |
| 9 | H, $CH_2$ (**1a**) | H, H, Br (**5f**) | **6i**: 77 | 99 |
| 10 | H, $CH_2$ (**1a**) | H, H, $NO_2$ (**5g**) | **6j**: 84 | >99 |

[a] Reactions were performed on a 0.1 mmol scale. Absolute configuration was determined by X-ray crystallography analysis of a derivative of **6c** and the remaining structures were assigned by analogy (see the Supporting Information for details). [b] Determined by UPC$^2$ using a chiral stationary phase.

was investigated, and it was found that several aldehydes gave their respective products (**6a–d**) in good yields and excellent enantioselectivities (entries 1–4). Likewise, a series of allylic acetates were evaluated in the reaction and were found to provide similar results (entries 5–10).

It should be noted that for the palladium-catalyzed γ-allylation, low yields were achieved by using allylic alcohols (**2**) as the reaction partner, thus allylic acetates (**5**) were employed. This change in substrate raises the question as to whether the observed regioselectivity is governed by the metal catalyst or the connectivity of the allylic reaction partner by the presence of a so-called "memory effect".[17] To address this issue, control experiments using a branched allylic acetate and a primary allylic alcohol under the respective developed reaction conditions were performed. These revealed that the regioselectivity of the reaction is controlled exclusively by the metal catalyst (see the Supporting Information).

In summary, we have developed the first asymmetric γ-allylation of α,β-unsaturated aldehydes based on combined organocatalysis and transition-metal catalysis. Whereas the employment of an iridium catalyst allows selective access to both diastereomers of branched products in excellent regio- and stereoselectivities, the linear products can be accessed in good yields and excellent regio- and enantioselectivities by the use of a palladium catalyst. The developed method thus provides selective access to all six isomers of γ-allylated product in a divergent fashion by the application of the appropriate combination of aminocatalyst, transition-metal catalyst, and ligand.

**Keywords:** allylation · asymmetric catalysis · diastereodivergence · dual catalysis · regiodivergence

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