

Bicyclic Guanidine-Catalyzed Direct Asymmetric Allylic Addition of *N*-Aryl Alkylidene-Succinimides

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The enantioselective functionalization of allylic positions has attracted the attention of organic chemists owing to the broad synthetic potential of the product, functionalized enantio-enriched alkenes.^[1] Transition-metal-catalyzed asymmetric allylic alkylation is the most developed strategy in allylic transformations and its popularity is due to its tolerance to a variety of functional groups and its flexibility in diverse bond constructions.^[2] However, the conspicuous drawbacks of transition-metal-catalyzed allylic alkylation include the use of toxic and expensive metals and the generation of a stoichiometric amount of waste, the leaving group. To avoid using transition metals, other strategies with chiral allylsilanes, allylboronates, and allylboranes were also developed.^[3] Recent improvements include the use of chiral BINOL-derived diols to catalyze the highly enantioselective asymmetric allylboration of ketones.^[4] In addition, Lewis acidic indium complexes with low toxicity were found to be efficient catalysts for the asymmetric C–C bond formations between hydrazones and allyl boronates.^[5]

Recently, direct allylation reactions using all carbon allylic nucleophiles have attracted considerable attention. For example, the direct asymmetric addition of allyl cyanides or β,γ -unsaturated esters to different electrophiles was successful using soft Lewis acid/hard Brønsted base cooperative catalysts.^[6] Alternatively, organocatalytic approaches were

investigated for the γ -functionalization of α,β -unsaturated carbonyl compounds.^[7] Addition of alkylidene cyanoacetates to acrolein was reported that utilized cinchona alkaloids as chiral bases.^[8] Carbonyl allylation of methyl trifluoropyruvate with activated alkenes by non-chiral organobases was also described.^[9] For the above-mentioned examples, strong electron-withdrawing groups were required to activate the olefin to enhance the acidity of the allylic protons. The resulting regioselectivity for either α - or γ -addition, depends on the combination of substrates and the catalyst used.

Previously, we have successfully demonstrated that *N*-aryl methylidene-succinimides (*N*-aryl itaconimides) were good electrophiles in enantioselective protonation reactions.^[10] In the transformation, we observed that isomerization of the alkene moiety in these methylidene-succinimides could occur and led to the thermodynamically more stable maleimide derivatives under basic conditions (Figure 1). It was

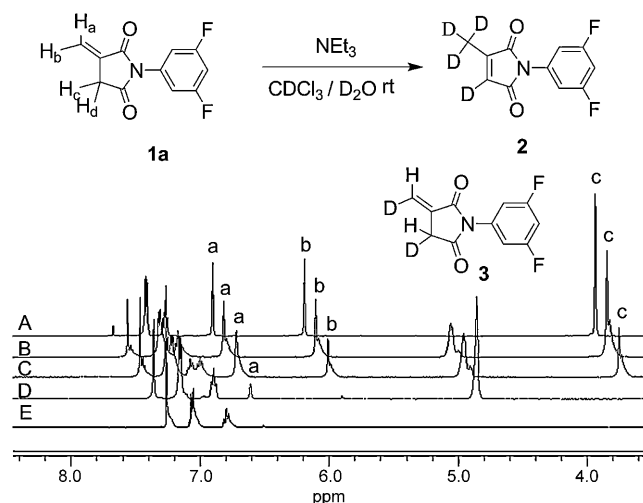


Figure 1. Deuteration reaction of **1a** studied by NMR spectroscopy. The reaction was carried out using 0.02 mmol of **1a** and Et₃N in 2 mL CDCl₃ and 1 mL D₂O. A) **1a** before deuteration; B) 6 h; C) 24 h; D) 48 h; E) one week.

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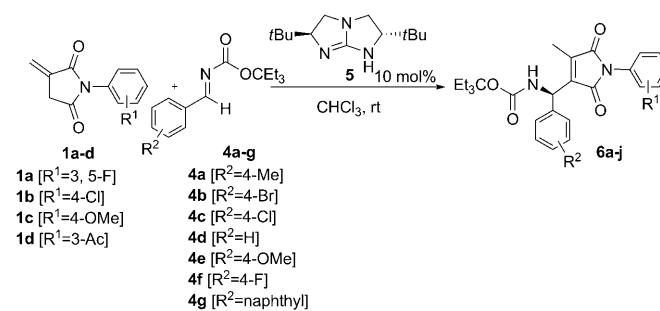
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hypothesized that the α -protons of these methyldene-succinimides were acidic enough to be activated by an organobase. To support this hypothesis, a deuteration–isomerization experiment was designed. A 1:1 mixture of *N*-(3,5-difluorophenyl)methyldene-succinimide (**1a**) and triethylamine was monitored in a solvent mixture of $\text{CDCl}_3/\text{D}_2\text{O}$ (3:1) by NMR spectroscopy. Results indicated that both the α -protons and γ -protons in methyldene-succinimide **1a** were deuterated under these basic conditions. Further analysis of the isomerization process revealed the existence of intermediate **3**. After 6 h, the ratio between protons a, b, and c (see Figure 1) was observed to be 1:0.5:1 and this provided support for this intermediate. As the reaction time increased, the equilibrium shifted towards maleimide **2** and full deuteration was achieved for all protons.

Encouraged by this observation, we envisioned a Brønsted-base catalyzed asymmetric allylic addition using *N*-aryl alkylidene-succinimides as nucleophiles. We have shown previously that chiral guanidine^[11] can catalyze a variety of reactions with high enantioselectivities. Herein, we demonstrate that bicyclic guanidine can catalyze the direct asymmetric allylic addition of *N*-aryl alkylidene-succinimides to imines with high enantioselectivities.

Preliminary studies using methyldene-succinimide **1a** revealed that direct allylic addition to *N*-protected imines resulted in amine **6g** as the only product by an α -addition followed by a 1,3-proton shift (Scheme 1). No product resulting

Table 1. α -Selective direct allylation reaction of 2-methyldene-*N*-aryl succinimide **1a** with *N*-Eoc imines.



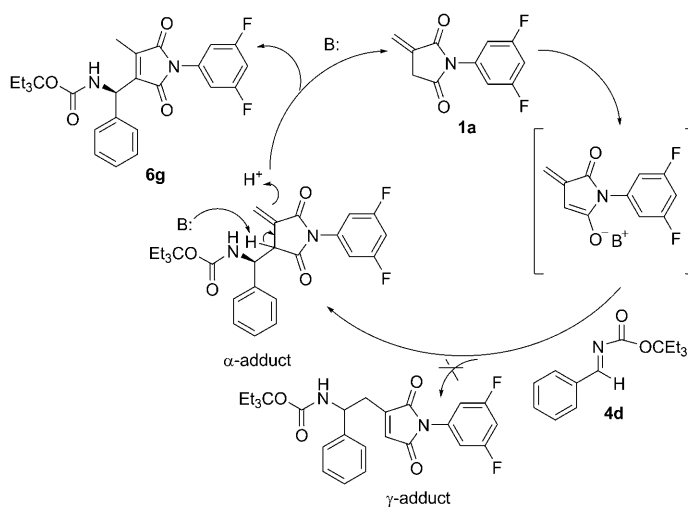
Entry	1	2	Product	Time [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	1b	4a	6a	24	92	86
2	1c	4a	6b	48	80	84
3	1d	4a	6c	24	83	81
4	1a	4a	6d	10	92	87
5	1a	4b	6e	10	90	77
6	1a	4c	6f	10	90	77
7	1a	4d	6g	10	91	83
8	1a	4e	6h	10	90	87
9	1a	4f	6i	10	91	82
10	1a	4g	6j	10	91	81

[a] Yield of isolated product. [b] Determined by chiral HPLC. Absolute configurations were determined by X-ray structure analysis (see the Supporting Information).

background reaction, namely the isomerization of the succinimides to maleimides. The substituents on the phenyl ring affected the reaction rates as well as enantioselectivities (Table 1, entries 1–4). Among these substituents, **1a** bearing a 3,5-difluorophenyl aryl group resulted in adducts with the highest enantiomeric excess. Thus, methyldene-succinimide **1a** was selected to investigate the reaction with a series of *N*-Eoc imines (Table 1, entries 5–10). No γ -addition products were observed and good enantioselectivities were obtained with all of the imines.

Subsequently, we examined the influence of a substituted double bond on the succinimides towards this Mannich-type allylic addition reaction. *N*-Aryl benzylidene-succinimides **7a–c** (Table 2) were prepared in a simple, one-step and *E*-selective protocol.^[13] A 1,3-proton shift, after the initial addition, was no longer favorable due to this extra conjugation. A highly diastereoselective reaction was obtained with a diastereomeric ratio that was generally > 98:2. The *anti*-selective reaction provided rapid entry to amines with two contiguous chiral centers in high enantioselectivities.

When the phenyl group on the double bond was replaced with an ester group, the reaction rate was greatly enhanced (Table 3). Reactions were complete within 4 h even with a lower catalyst loading. The ratio of *N*-Eoc imines was reduced to 1.5 equivalents without detecting any isomerized product. However, the enantioselectivities were compromised. Only the α -addition product was observed with a 1,3-proton shift reaction proceeding favorably to provide maleimides **10a–g**.



Scheme 1. Proposed reaction sequences of α -selective direct allylation reaction of methyldene-succinimide **1a**.

from the γ -addition was observed. *N*-3-Ethylpentan-3-yloxy-carbonyl (Eoc) imines were previously shown by our group to be excellent electrophiles in bicyclic guanidine-catalyzed enantioselective Mannich reactions. They were also crucial in this experiment in improving enantioselectivities.^[12]

In the presence of 10 mol % of guanidine **5**, *N*-aryl methyldene-succinimides **1a–d** added to *N*-Eoc imines with high regio- and enantioselectivities (Table 1). However, three equivalents of imines were required to compete with the

Deuterium-labeling studies of the reaction products and intermediates in catalytic reactions can provide valuable information on the reaction pathways and the structure of the intermediates.^[14] For this reaction, useful deuterations were achieved by labeling the substrate,^[15] the catalyst,^[16] or the solvent.^[17] Several reactions were investigated by this method and they include hydrogenation,^[18] the aza-MBH-type reaction,^[19] asymmetric allylic alkylation,^[20] and hydration.^[21]

To gain further insight into the mechanism, deuterium-labeling experiments were carried out using a mixture of organic solvent and D₂O. Methylidene-succinimide **1a** yielded a terminal deuterated adduct **11** with a single deuterium labeled on the terminal methyl group [Eq. (1)]. This deuterium most likely resulted from a 1,3-proton shift and the terminal methyl was not expected to be acidic enough to undergo further deuteration. Benzylidene-succinimide **7a** provided an enantio-enriched α -deuterium, β -amine adduct [Eq. (2)]. The stabilizing effects of the phenyl substituent on the double bond, through conjugation, prevented the isomerization process from occurring. On the other hand,

deuteration of the two γ -protons on **13** indicated that either the isomerization of the double bond from exocyclic to endocyclic was reversible or that the α -protons next to the ester group were sufficiently acidic to be replaced under the reaction conditions [Eq. (3)].

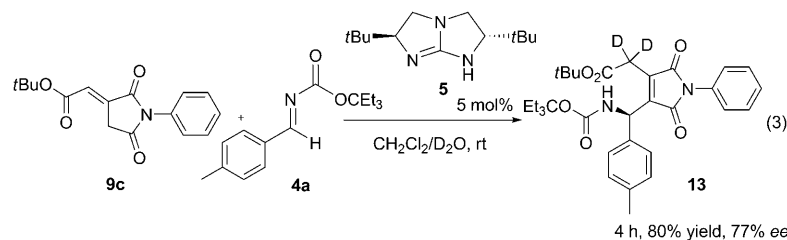
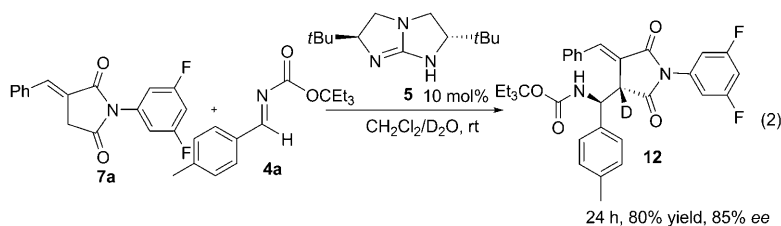
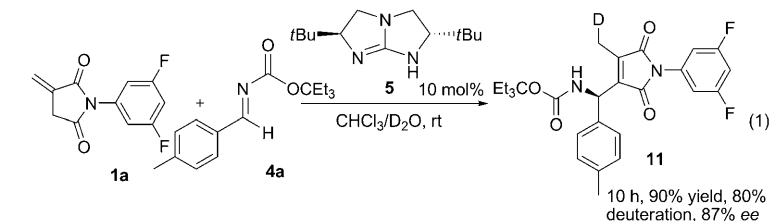
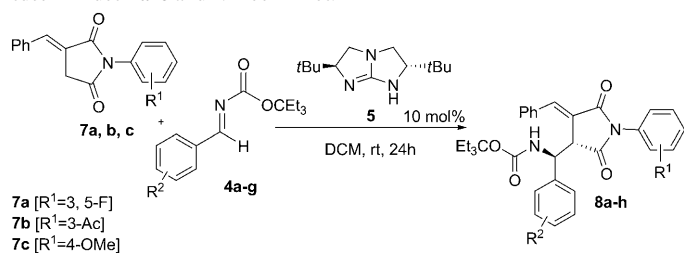


Table 2. Mannich-type allylic addition between *N*-aryl benzylidene-succinimides **7a–c** and *N*-Eoc imines.

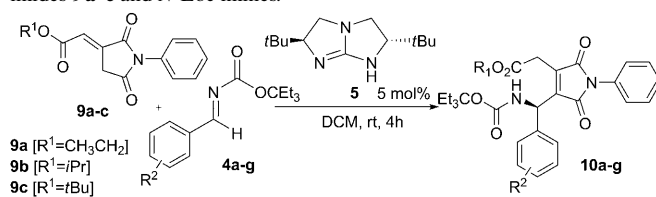


7a [R¹=3, 5-F]
7b [R¹=3-Ac]
7c [R¹=4-OMe]

Entry	1	2	Product	Yield [%] ^[a]	d.r. ^[b]	ee [%] ^[b]
1	7a	4a	8a	80	99:1	85
2	7b	4a	8b	82	98:2	84
3 ^[c]	7c	4a	8c	83	99:1	83
4	7a	4b	8d	84	91:9	78
5	7a	4d	8e	90	99:1	85
6	7a	4e	8f	80	99:1	85
7	7a	4f	8g	83	87:13	82
8	7a	4g	8h	81	99:1	84

[a] Yield of isolated product. [b] Determined by chiral HPLC, the relative configurations of the two consecutive chiral centers were determined by X-ray structure analysis (see the Supporting Information). [c] Reaction time was 48 h.

Table 3. Mannich-type allylic addition between *N*-aryl esterlidene-succinimides **9a–c** and *N*-Eoc imines.



9a [R¹=CH₃CH₂]
9b [R¹=*i*-Pr]
9c [R¹=*t*-Bu]

Entry	R ¹	R ²	Product	Yield [%] ^[a]	ee [%] ^[b]
1	9a	4a	10a	92	71
2	9b	4a	10b	90	80
3	9c	4a	10c	92	77
4	9b	4b	10d	84	71
5	9b	4d	10e	88	75
6	9b	4f	10f	83	73
7	9b	4g	10g	86	70

[a] Yield of isolated product. [b] Determined by chiral HPLC, absolute configurations were determined by X-ray structure analysis (see the Supporting Information).

In summary, we have successfully developed a direct asymmetric allylic addition reaction to imines. This reaction provides enantio-enriched maleimides and succinimides that can be used to prepare aza-heterocycles with multiple chiral centers. NMR studies and deuterium-exchange experiments were used to study the intermediates in the reaction.

Experimental Section

General procedure for the bicyclic guanidine-catalyzed allylic addition of *N*-aryl methylidene-succinimide **1a to *N*-3-ethylpentan-3-yloxycarbonyl (Eoc) imine **4a**:** *N*-3-Ethylpentan-3-yloxycarbonyl (Eoc) imine **4a** (0.015 mmol) and catalyst **5** (1.14 mg, 0.005 mmol) was dissolved in chloroform (0.5 mL). *N*-3,5-Difluorophenylmethylidene-succinimide **1a** (0.05 mmol) was added to the reaction mixture after 5 min. The reaction mixture was monitored by TLC and upon complete consumption of **1a**, the solvent was removed under vacuum. The crude product was directly loaded onto a short silica gel column, followed by gradient elution with hexane/ethyl acetate = 20/1 to 12/1 to provide product **6d**.

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