Asymmetric Organocatalysis

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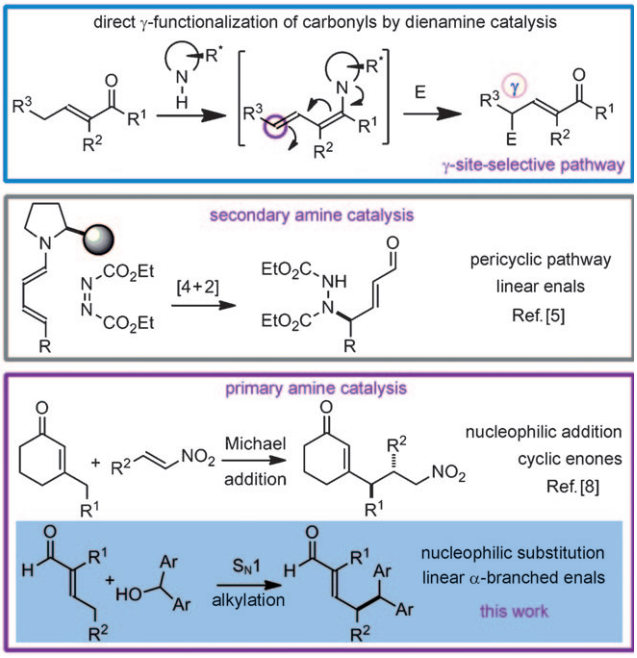
Cooperative Organocatalysis for the Asymmetric γ Alkylation of α-Branched Enals**

*Giulia Bergonzini, Silvia Vera, and Paolo Melchiorre**

The direct, catalytic, and stereoselective functionalization of carbonyl compounds at the γ position represents a highly challenging and persistent problem for asymmetric synthesis.[1,2] All attempts to solve this problem must address the challenge of site selectivity as well as stereoselectivity.[3] Recently, our research group hypothesized whether dienamine catalysis could provide a general platform for designing direct vinylogous processes,[4] by exploiting the ability of chiral amine catalysts to form a nucleophilic dienamine intermediate in situ in the condensation with γ-enolizable unsaturated carbonyl compounds. Dienamine catalysis was introduced in 2006 by Jørgensen and co-workers[5] to promote the direct, enantioselective γ amination of α,β-unsaturated aldehydes. However, it has since found limited application.[6] A recently published perspective on the advent of organocatalysis did not number dienamine catalysis among the generic modes of activation and induction.[7] This was probably a result of the fact that γ amination of enals was originally thought to follow a particular [4+2] cycloaddition path,[5] instead of a more general nucleophilic addition manifold.

Recently, we documented that dienamine catalysis can be exploited to promote vinylogous nucleophilicity within Michael addition patterns, upon selective activation of unmodified cyclic α,β-unsaturated ketones by primary amine catalysts.[8] Herein, we report that vinylogous reactivity induced by dienamine catalysis also has synthetic potential for nucleophilic substitution reactions. Specifically, we describe the direct asymmetric γ alkylation of α-substituted linear α,β-unsaturated aldehydes through an S_N1 pathway. This unprecedented transformation[9] has been accomplished using an interwoven activation pathway that successfully integrates dienamine catalysis and Brønsted acid catalysis[10] simultaneously.

The alkylation of carbonyl compounds is the archetypal nucleophilic substitution reaction. Recently, we and others have independently established the possibility of intercepting in situ generated stable carbocations with enamine intermediates, thereby leading to the challenging asymmetric α alkylation of aldehydes through an S_N1 pathway.[11] With the aim of applying the dienamine-induced vinylogous nucleophilicity within a substitution pattern, we focused on the S_N1-type γ alkylation of unmodified unsaturated carbonyl compounds (Scheme 1).



Scheme 1. Dienamine catalysis and the concept of vinylogy. E = electrophile.

As a model reaction, we chose the direct γ-alkylation of α-branched aldehyde **3** with bis(4-dimethylaminophenyl)methanol **4**, which can easily form a stabilized benzhydryl carbocation in situ[11b,12] under acidic conditions (Table 1). Recently, we established the unique ability of 9-amino-9-deoxy-*epi*-cinchona alkaloids (chiral primary amines easily derived from natural sources)[13] to efficiently activate sterically hindered carbonyl compounds, while imparting unconventional reactivity profiles (e.g. vinylogous nucleophilicity upon condensation with cyclic enones).[8] Moreover, this class of catalysts can activate the usually unreactive α-branched enals toward cascade reactions, thus combining orthogonal aminocatalytic modes.[13c] The versatility of this catalyst framework prompted us to explore its behavior in the context of the elusive γ-site activation of α-substituted linear α,β-unsaturated aldehydes under dienamine catalysis. Indeed,

[*] Prof. Dr. P. Melchiorre
ICREA—Institució Catalana de Recerca i Estudis Avançats
Passeig Lluís Companys 23-08010 Barcelona (Spain)
G. Bergonzini, Dr. S. Vera, Prof. Dr. P. Melchiorre
ICIQ—Institute of Chemical Research of Catalonia
Avenida Països Catalans 16-43007 Tarragona (Spain)
E-mail: pmelchiorre@iciq.es
Homepage: http://www.iciq.es/portal/862/Melchiorre.aspx

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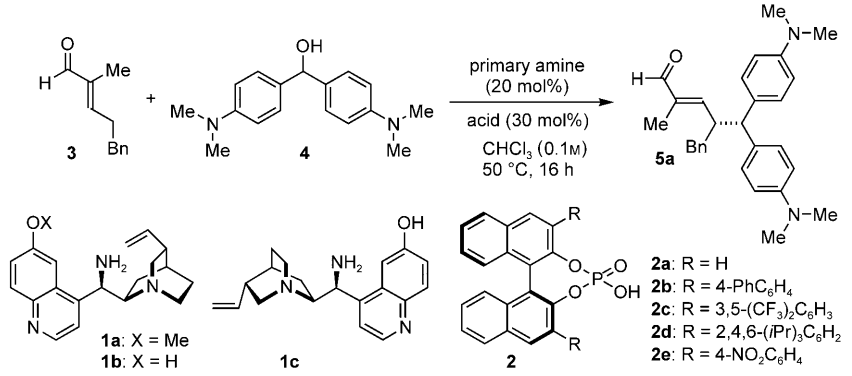
Table 1: Development of a cooperative organocatalytic system for the direct γ-alkylation of α-branched enals.[a]



Entry	Primary amine	Brønsted acid	Conv [%][b]	*ee* [%][c]
1	**1a**	TFA	28	< 5
2	**1b**	TFA	75	60
3	**1b**	(*S*)-**2a**	> 95	80
4	**1b**	(*S*)-**2b**	8	n.d.
5	**1b**	(*S*)-**2c**	4	n.d.
6	**1b**	(*S*)-**2d**	5	92
7	**1b**	(*S*)-**2e**	62	93
8[d]	**1b**	(*S*)-**2a**	> 95 (82)	90
9[d]	**1b**	(*S*)-**2e**	93 (84)	95
10[d]	**1c**	(*R*)-**2e**	> 95 (89)	90[e]
11	**1b**	(*R*)-**2e**	30	21[e]
12	**1c**	(*S*)-**2e**	24	< 5
13	benzyl amine	(*S*)-**2a**	33	14

[a] Reactions carried out using 3 equivalents of enal **3**. ^{1}H NMR analysis of the crude mixture indicated a highly γ-site-selective alkylation pathway. Other products arising from different reaction manifolds (e.g. α alkylation under enamine catalysis) were sporadically detected in negligible amounts. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis on chiral stationary phases. [d] Reactions carried out using 15 mol% of **1** and 30 mol% of **2** and 2 equivalents of enal **3**. Numbers in parenthesis refer to yield of isolated **5a**. [e] The opposite *S* enantiomer of **5a** was obtained. The absolute configuration of **5a** was established by chemical correlation (see the Supporting Information for details). Bn = benzyl, TFA = trifluoroacetic acid.

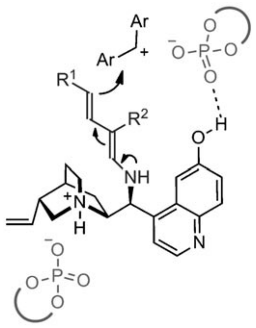
20 mol% of catalyst **1a**, which is directly derived from quinidine, in combination with 30 mol% of TFA as the acidic co-catalyst, led to compound **5a** as the unique product of the process, albeit with essentially no stereocontrol (Table 1, entry 1).[14] However, we were encouraged by the power of primary amine catalysis to direct the reaction manifold toward a γ-site-selective alkylation. Indeed, the use of bifunctional primary amine 6′-hydroxy-9-amino-9-deoxy-*epi*-quinidine[8,15] **1b** dramatically increased the enantioselectivity as well as the reaction rate of the vinylogous alkylation while maintaining complete γ selectivity (Table 1, entry 2).

To improve the level of stereocontrol, we envisioned the possibility of integrating dienamine catalysis and chiral Brønsted acid catalysis. A phosphoric acid can induce the formation of a chiral contact ion-pair from alcohol **4**[16], which may synergistically engage in a matched combination with the chiral covalent dienamine intermediate that arises from the condensation of the primary amine with enal **3**. To pursue this cooperative prospect,[17] we combined **1b** with the simple and easily available phosphoric acid (*S*)-**2a**, thereby greatly improving the enantioselectivity to a practical level (Table 1, entry 3).[18]

Structural modification of the Brønsted acid catalyst **2** revealed a strong correlation between the acidity and the reactivity—as is strictly related to the ability to induce in situ carbocation formation (Table 1, entries 3–7). Catalyst **2e** led to an increase of the enantioselectivity to 92% *ee*. Finally, a 1:2 ratio of amine to acid combination maximized the synergistic effects of the cooperative catalysts (Table 1, entries 8 and 9). Interestingly, the opposite configuration of the product can be accessed by simply selecting the appropriate enantiomer of the catalyst. Thus, combining the pseudoenantiomeric catalyst **1c**, derived from quinine, with (*R*)-**2e** afforded **5a** with opposite absolute configuration while maintaining a high level of selectivity (Table 1, entry 10).

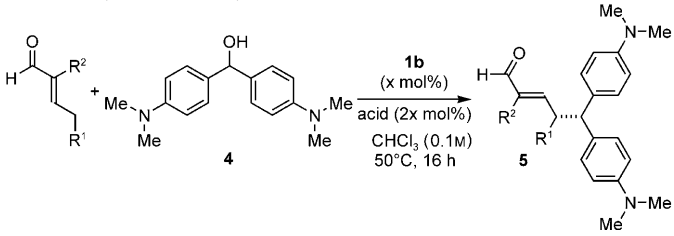
To gain insight into the specific role of each individual activation pathway, we used the mismatched catalyst combinations to promote the γ alkylation of **3** with **4** (Table 1, entries 11 and 12). This combination resulted in a dramatic loss of reactivity and enantioselectivity. Moreover, the results obtained when dienamine and Brønsted acid catalysis were operating individually (Table 1, entries 2 and 13) further supported a highly constructive and synergic cooperation in the presence of the matched-pair combination. These observations provoke interesting mechanistic considerations. We believe that the primary amine activates the enal moiety toward vinylogous nucleophilicity by means of dienamine catalysis, while the chiral phosphate anion that arises from **2** has the dual role of acting as counter anion for both the protonated quinuclidine moiety (within the cinchona scaffold) and the benzhydryl cation formed in situ. Moreover, the great influence of the hydrogen-bond donor at the 6'-position of the primary amine **1b** on both reactivity and stereoselectivity of the γ alkylation prompted us to propose a mechanistic model in which both the electrophilic and nucleophilic chiral intermediates interact through a network of noncovalent interactions, as depicted in Scheme 2.[19]

The dual-catalyst system was then applied to the direct γ-alkylation of a variety of α-branched γ-enolizable enals.[20] The results reported in Table 2 illustrate how different substituents at the γ position can be accommodated without affecting either the site selectivity or the enantioselectivity of the S_N1 alkylation (Table 2, entries 1–6). Use of the substituted phosphoric acid **2e** instead of the simple acid **2a** led to higher levels of stereocontrol (Table 2, entries 2, 3, and 5).



Scheme 2. Proposed mechanistic model.

Table 2: Asymmetric γ alkylation of α-branched enals.[a]

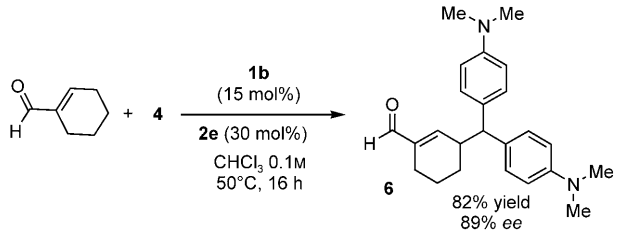


Entry	R^1	R^2	x [mol%]	2	Product	Yield [%][b]	*ee* [%][c]
1	Bn	Me	15	**2a**	**5a**	82	90
2	Bn	Me	15	**2e**	**5a**	84	95
3	Me	Me	15	**2e**	**5b**	98	89
4	allyl	Me	20	**2a**	**5c**	91	87
5	allyl	Me	15	**2e**	**5c**	65	94
6	*i*Pr	Me	20	**2a**	**5d**	80	87
7	Et	Et	20	**2a**	**5e**	58	82
8	Bn	Et	20	**2a**	**5f**	82	72
9	Bn	Bn	20	**2a**	**5g**	72	73
10	Me	Ph	20	**2a**	**5h**	71	45
11[d]	Ph	Me	15	**2a**	**5i**	63	90
12[d]	*p*-ClC_6H_4	Me	20	**2a**	**5j**	61	82
13[d]	*p*-$MeOC_6H_4$	Me	20	**2a**	**5k**	72	86

[a] Reactions carried out using 2 equivalents of enal. ^{1}H NMR analysis of the crude mixture indicated a highly γ-site-selective alkylation pathway. Quinidine-derived primary amine **1** and the *S* enantiomer of chiral phosphoric acids **2** were used. [b] Yield of the isolated compounds **5**. [c] Determined by HPLC analysis on a chiral stationary phases. [d] Reactions carried out at 10°C.

There appears to be remarkable latitude in the electronic and steric demands of the aldehydic component (Table 2, entries 7–13). Different aliphatic substituents and even a phenyl group in the α position of the enals are well-tolerated, thus enabling access to a broad variety of multifunctional molecules with complete γ-site selectivity and moderate to high levels of enantioselectivity. Remarkably, when R^1 is an aromatic group (Table 2, entries 11–13), the γ-alkylation protocol opens direct access to enantioenriched benzylic carbon stereocenters.

Finally, we explored the possibility of extending primary-amine-induced vinylogous nucleophilicity to 1-cycloalkene-1-carboxaldehyde. The cooperative catalysis system afforded the γ-alkylation product **6** with high regio- and enantioselectivity (Scheme 3).



Scheme 3. Primary-amine-catalyzed γ alkylation of 1-cycloalkene-1-carboxaldehyde.

In summary, the reported γ-site-selective alkylation of α-branched enals represents the first example of a catalytic, asymmetric vinylogous substitution reaction of unmodified carbonyl compounds. This unprecedented chemical transformation affords functionalized compounds ready for further manipulation at the α and β positions, even through appealing cascade sequences. This study confirms the ability of chiral primary amine catalysis to impart unique reactivity profiles with challenging compound classes such as α-branched enals. Here, dienamine catalysis has been exploited to promote vinylogous nucleophilicity within substitution reaction manifolds. Given the versatility of chiral phosphoric acids in electrophilic activation, we believe that the cooperative catalysis system involving dienamine catalysis and Brønsted acid catalysis will find applications for other asymmetric γ functionalization of carbonyl compounds.

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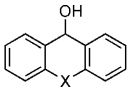

X = S, 48% yield, 48% *ee*
X = O, 82% yield, 29% *ee*

