Secondary Amine-Catalyzed Asymmetric γ-Alkylation of α-Branched Enals *via* Dienamine Activation

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Dedicated to *Dieter Seebach* on the occasion of his 75th birthday

The direct and enantioselective γ-alkylation of α-substituted α,β-unsaturated aldehydes proceeding under dienamine catalysis is described. We have found that the *Seebach* modification of the diphenylprolinol silyl ether catalyst in combination with saccharin as an acidic additive promotes an S_N1 alkylation pathway, while ensuring complete γ-site selectivity and a high stereocontrol. Theoretical and spectroscopic investigations have provided insights into the conformational behavior of the covalent dienamine intermediate derived from the condensation of 2-methylpent-2-enal and the chiral amine. Implications for the mechanism of stereoinduction are discussed.

Introduction. – Asymmetric amine catalysis has greatly expanded the chemist's ability to stereoselectively functionalize unmodified CO compounds[1]). Over the past decade, enamine[2]), and iminium-ion[3]) activations have become reliable synthetic platforms for generating stereogenic centers at the α- and β-positions of CO compounds with very high fidelity. More recently, the chemists' interest has shifted toward the use of amine catalysis for targeting ever more remote stereogenic centers[4]). Moving along the chain of a CO substrate requires the propagation of the electronic effects inherent to enamine and iminium-ion activations (*i.e.*, the HOMO-raising and the LUMO-lowering effect, resp.) through the conjugated π-system of poly-unsaturated CO compounds[5]). The first success in the design of direct vinylogous processes[6]) was achieved by means of dienamine activation of γ-enolizable unsaturated CO compounds. Introduced in 2006 by *Jørgensen* and co-workers [8] to promote the

[1]) For recent reviews on amine catalysis, see [1a][1b]. For insightful perspectives on amine catalysis mediated by secondary amines, see [1c–1e].

[2]) For the pioneering study, see [2a]. For a review on enamine activation: see [2b].

[3]) For the pioneering study, see [3a]. For a review on iminium-ion activation: see [3b].

[4]) For an overview, see [4a]. For a discussion on the mechanisms of amine catalysis by secondary amines, see [4b].

[5]) Propagation of the HOMO-raising effect: for *dienamine activation*, see [5][6]. For *trienamine activation*, see [7a][7b]. For our contribution, see [7c]. Propagation of the LUMO-lowering effect: for *vinylogous iminium-ion activation*, see [7d].

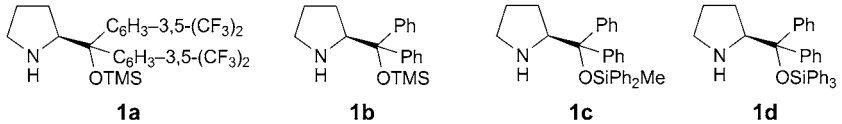
[6]) Vinylogous reactivity is defined as the transmission of electronic effects through a conjugated π-system [5a]. For a review on dienamine activation, see [5b].

enantioselective γ-amination of α,β-unsaturated aldehydes under the catalysis of the diaryl-prolinol silyl ether **1a** [9], dienamine activation exploits the intrinsic vinylogous nucleophilicity of the *in situ* generated dienamine intermediate. Surprisingly enough, this activation mode has since found limited application in asymmetric synthesis [6][7]), probably because γ-amination of enals under secondary-amine catalysis was originally proposed to follow a particular [4 + 2] cycloaddition path [8] instead of a more general nucleophilic addition manifold.

We recently demonstrated that primary-amine catalysis, specifically the use of cinchona-based amine of type **2** [10], can greatly expand the synthetic potential of dienamine activation, promoting vinylogous nucleophilicity within *Michael* addition patterns, upon selective activation of unmodified cyclic α,β-unsaturated ketones [11].

The logical extension to consolidating dienamine catalysis as a useful template for the γ-functionalization of unmodified CO compounds was its application to nucleophilic substitution reactions[8]). We found that 9-amino-6′-hydroxyquinidine **2a** successfully catalyzed the direct asymmetric S_N1-type γ-alkylation [12] of α-substituted linear α,β-unsaturated aldehydes **3** with bis[4-(dimethylamino)phenyl]methanol **4a**[9]), which can easily form *in situ* a stabilized benzhydryl carbocation under acidic conditions [14]. Achieving a high level of enantioselectivity in the γ-alkylated compound **5** (up to 95% ee) required the combination of the primary amine **2a** with a chiral phosphoric acid in order to integrate dienamine activation and *Brønsted* acid catalysis simultaneously (*Scheme 1*, *a*) [15].

At the same time, an independent study by *Christmann* and co-workers established the ability of secondary-amine catalyst, specifically the diphenylprolinol silyl ether **1b** (the *Jørgensen–Hayashi* catalyst) and its analog **1a**, to promote the same S_N1-type alkylation of unsubstituted linear enals (*Scheme 1*, *b*). However, the catalytic system provided moderate control over the site selectivity (competing α- *vs.* γ-site alkylation) and a high level of stereocontrol only for selected examples [16].



1a **1b** **1c** **1d**

1e **1f** **1g** **1h**

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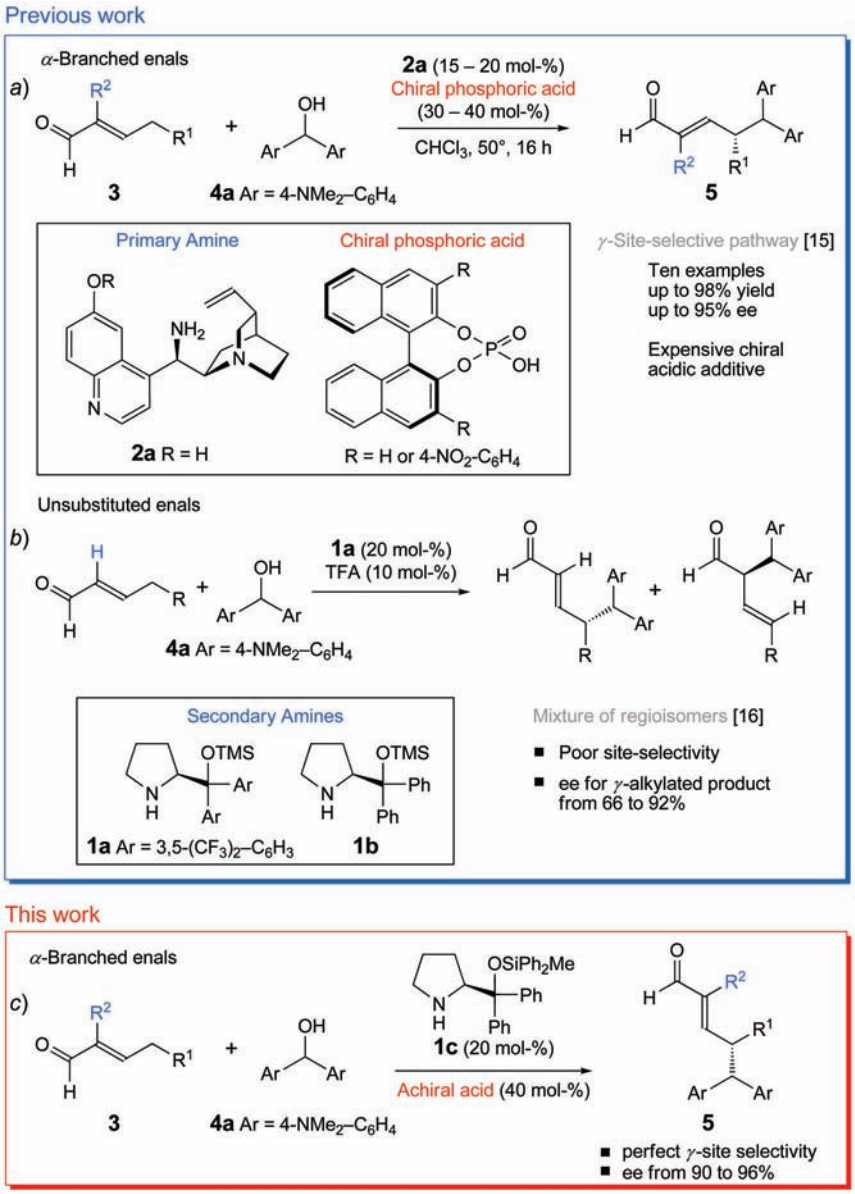
7) For selected examples using secondary-amine catalysis, see [6].

8) The alkylation of CO compounds is the archetypal nucleophilic substitution reaction. Recently, our group [12] and others [13], independently, have established the possibility of intercepting *in situ* generated stable carbocations with catalytic enamine intermediates, leading to the challenging asymmetric α-alkylation of aldehydes *via* an S_N1 pathway.

9) The *in situ* formation under acidic conditions of stabilized benzhydryl carbocation from **4** has been used for the α-alkylation of aldehydes *via* enamine catalysis. For the pioneering work, see [13a]. For related studies, see [13b]. For a recent highlight, see [13c].

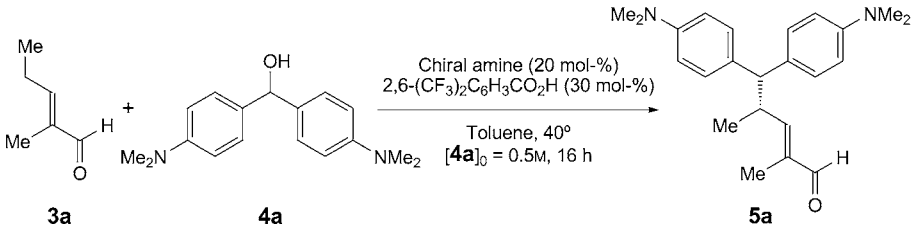
Scheme 1. *Vinylogous Substitution Reaction in the* S_N1*-Type* γ*-Alkylation of Enals* via *Dienamine Activation. a*) Primary-amine activation of α-branched enals: cooperative dual catalysis system between dienamine and *Brønsted* acid catalysis [15]. *b*) Secondary-amine activation of linear enals [16]. *c*) Secondary-amine activation of α-branched enals.



Herein, we report a novel, convenient, and effective catalytic system for the direct asymmetric γ-alkylation of α-branched enals **3** *via* an S_N1 pathway (*Scheme 1,c*). We have found that the amine **1c**, the *Seebach* modification of the *Jørgensen–Hayashi* catalyst [17a][10]), in the presence of an *achiral* acid additive, induces perfect γ-site selectivity and very high enantioselectivity (up to 96% ee). Synthetically, the present method outperforms the catalytic system previously reported by us [15], since a single chiral entity is required. This study also offers the first evidence for the unanticipated power of secondary-amine catalysis to induce vinylogous nucleophilicity through dienamine activation of sterically hindered CO compounds, such as α,β-disubstituted enals **3**.

Results and Discussion. – As a model reaction, we chose the direct γ-alkylation of 2-methylpent-2-enal (**3a**) with bis[4-(dimethylamino)phenyl]methanol (**4a**; *Table 1*). The standard in terms of efficiency and enantioselectivity for this transformation has been set during our previous investigations on cinchona-based primary-amine catalysis [15]. The quinidine-derived amine **2a** (15 mol-%) required the presence of a chiral phosphoric acid co-catalyst (30 mol-%) to attain synthetically useful results, affording

Table 1. *The Model Reaction for the Direct γ-Alkylation of α-Branched Enals and the Catalysts Tested*[a])



3a **4a** **5a**

Entry	Catalyst	Yield [%][b])	ee [%][c])
1[d])	**2a**	98	89 [15]
2	**1a**	3	75
3	**1b**	10	81
4	**1c**	18	88
5	**1d**	13	84
6	**1e**	3	71
7	**1f**	n.r.	–
8	**1g**	n.r.	–
9	**1h**	n.r.	–

[a]) Reactions performed at 40° on a 0.1-mmol scale, with 2 equiv. of enal **3a** with $[\mathbf{4a}]_0 = 0.5$M in toluene, without any precaution for excluding air. [b]) Determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard; n.r. = no reaction. [c]) Determined by HPLC analysis on a chiral stationary phase. [d]) Reaction conducted in $CHCl_3$ at 50° and catalyzed by the combination of 15 mol-% of the primary amine **2a** and 30 mol-% of the chiral phosphoric acid. Result taken from [15].

[10]) For an application of catalyst **1c** in conjugate addition to enals under iminium ion activation, see [17b].

the product **5a** in almost quantitative yield and 89% of enantiomeric excess (ee; *Table 1*, *Entry 1*). In this dual-catalyst system, the enantioselectivity was found to be significantly higher, when a chiral phosphoric acid was used in place of an achiral co-catalyst such as CF_3COOH (TFA; 60% ee; results taken from [15]). This indicated that the intrinsic potential of amine **2a** to forge the γ stereogenic center by means of dienamine activation was moderate.

The quest for a more convenient γ-alkylation protocol, based on the use of a single chiral entity, prompted us to undertake an extensive catalyst screening, detailed in *Table 1*. This study led to an unexpected observation: the commercially available diphenylprolinol silyl ether **1b** (*Jørgensen–Hayashi* catalyst) could indeed catalyze the process [18]. The combination of **1b** with 30 mol-% of 2,6-bis(trifluoromethyl)benzoic acid[11])[12]) led to compound **5a** as the unique product with good enantiomeric control, albeit with poor yield (*Entry 3*). This stands in contrast to the catalytic profiles of secondary amines that are generally unable to efficiently activate sterically hindered CO compounds, such as α,β-disubstituted enals [20][13]). Despite the poor reactivity initially achieved with catalyst **1b**, we were encouraged by the unanticipated ability of secondary-amine catalysis to direct the reaction manifold toward a γ-site-selective alkylation through dienamine activation of α-branched enals[14]).

Gratifyingly, both reactivity and stereocontrol were sensitive to catalyst structural modifications, the bulkier silyl protective group of catalyst **1c** leading to a significant improvement (compare *Entries 3* and *4*). This catalyst was first reported by *Seebach et al.* [17a], who predicted, based on the X-ray crystallographic analysis of the iminium-ion structure, a more effective shielding of the chiral fragment over the pro-chiral face of the reactive intermediate, in comparison with the standard Me_3Si (TMS) group within the catalyst **1b**. Further increasing the steric hindrance of the pendant silyl group did not provide higher stereoselectivity (*Entry 5*). Interestingly, other widely employed chiral secondary amines (proline or the second-generation *MacMillan* catalyst[15])) were not able to promote this transformation.

Further optimization studies were carried out with amine **1c** as the catalyst. Examination of the reaction media, detailed in *Table 2* (reactions performed at 25°), revealed the requirement for an apolar solvent in order to obtain high stereoselectivity.

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[11]) The nucleophilic dienamine generated by activation of enal **3a** undergoes the alkylation with the benzhydryl carbocation derived from acid-catalyzed ionization of bis[4-(dimethylamino)phenyl]-methanol **4a**. In the absence of any acids, the model reaction does not proceed.

[12]) The S_N1-type α-alkylation of aldehydes under enamine activation has been developed by using different methods to induce the ionization of the carbocation precursors. For the use of *Lewis* acids, see [19a]. For oxidative conditions, see [19b]. For preformed salts of the carbocation intermediate, see [19c].

[13]) Chiral secondary amines have found limited applications only in the iminium ion activation of hightly reactive α-branched acroleins, see, *e.g.*, [21a–c]. For the sole examples dealing with the iminium ion activation of α,β-disubstituted enals [21d][21e].

[14]) The activation of α,β-disubstituted enals generally requires chiral primary amines [20]. As far as we know, there are no published examples of dienamine activation of α,β-disubstituted enals by secondary-amine catalysis.

[15]) For excellent investigations on the relative reactivity of the covalent intermediates (enamines and iminium ions) derived from diphenylprolinol trimethylsilyl ether and the *MacMillan* imidazolinone catalysts, see [22].

Table 2. *Solvent Screening for the Model Reaction*[a])

Entry	Solvent	Dielectric constant (ε)[b])	Yield [%][c])	ee [%][d])
1	Hexane	2	5	87
2	Toluene	2.4	5	94
3	Et_2O	4	11	77
4	$CHCl_3$	5	10	81
5	CH_2Cl_2	9.1	18	81
6	MeCN	36	46	78

[a]) Reactions performed at 25° on a 0.1-mmol scale over 16 h, with 20 mol-% of amine **1c**, 30 mol-% of 2,6-bis(trifluoromethyl)benzoic acid, 2 equiv. of enal **3a** with $[\mathbf{4a}]_0 = 0.5$M in the specified solvent. [b]) Data taken from [23]. [c]) Determined by ^{1}H-NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard. [d]) Determined by HPLC analysis on a chiral stationary phase.

Solvents with a high dielectric constant strongly increased the reactivity but at the expense of the enantioselectivity.

We then found that the nature of the acidic additives was also crucial for modulating the catalyst efficiency, in particular in terms of reactivity. Upon investigation of a variety of acid co-catalysts (*Table 3*; reaction performed in toluene as the solvent), saccharin was identified as the most promising additive toward the design of an effective amine **1c**-based catalytic system (*Entry 9*).

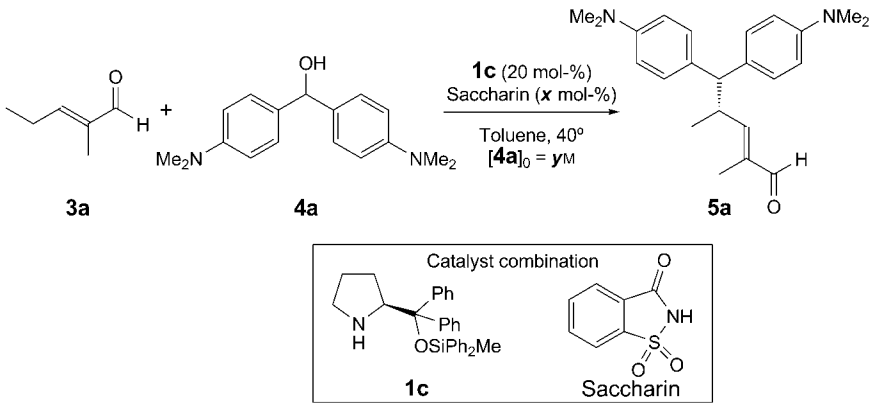
Table 3. *Acid Screening for the Model Reaction Carried Out in Toluene*[a])

Entry	Acid	Yield [%][b])	ee [%][c])
1	2,6-Bis(trifluoromethyl)benzoic acid	18	88
2	2,6-Difluorobenzoic acid	28	91
3	4-Nitrobenzoic acid	24	88
4	2-Nitrobenzoic acid	29	91
5	2,6-Dinitrobenzoic acid	83	82
6	Trifluoroacetic acid	29	88
7	*p*-Toluenesulfonic acid (TsOH)	6	71
8[d])	Diphenyl phosphate	27	91
9	Saccharin	71	88

[a]) Reactions performed at 40° on a 0.1-mmol scale, with 20 mol-% of amine **1c**, 30 mol-% of the acid, 2 equiv. of enal **3a** with $[\mathbf{4a}]_0 = 0.5$M in the specified solvent. Reaction time: 16 h. [b]) Determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]) Determined by HPLC analysis on a chiral stationary phase. [d]) Reaction carried out with 4 equiv. of **3a**.

A second cycle of optimization with 20 mol-% of the catalyst **1c** in toluene established a 2:1 saccharin/amine ratio as the most effective combination, while revealing that the reagent concentration was also crucial for modulating the efficiency (*Table 4*). Carrying out the reaction at 40° with an excess of enal **3a** (4 equiv.) while diluting the mixture ($[\mathbf{4a}]_0 = 0.25$M) provided the product **5a** with synthetically useful results over a 24-h reaction time (*Entry 8:* **5a** isolated in 88% yield and 93% ee). These conditions were selected to evaluate the scope of the secondary-amine-catalyzed γ-alkylation of α-branched enals.

Table 4. *Final Optimization Cycle*[a])



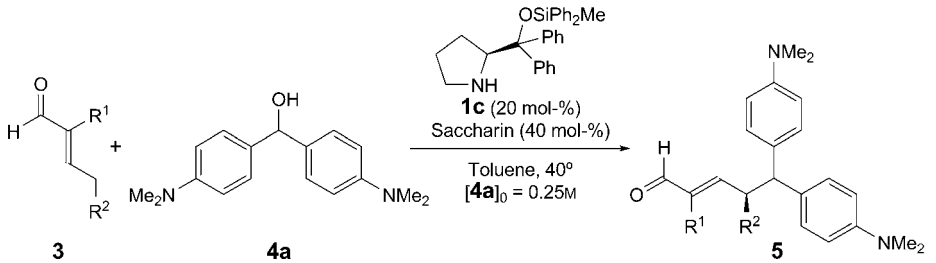
Entry	Saccharin (***x*** mol-%)	$[\mathbf{4a}]_0 = \boldsymbol{y}$M	*t* [h]	Yield [%][b])	ee [%][c])
1[d])	30	0.5	16	71	88
2	30	0.5	16	83	92
3	20	0.5	16	45	95
4	40	0.5	16	93	91
5	40	0.15	16	44	96
6	75	0.15	16	54	95
7	40	0.25	16	81	94
8	40	0.25	25	88[e])	93

[a]) Reactions performed at 40° on a 0.1-mmol scale, with 20 mol-% of amine **1c**, a variable amount of saccharin, 4 equiv. of enal **3a** in toluene. [b]) Determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]) Determined by HPLC analysis on a chiral stationary phase. [d]) Reaction carried out with 2 equiv. of **3a**. [e]) Value refers to the yield of the isolated compound **5a** after chromatographic purification.

As shown in *Table 5*, different alkyl substituents, including a heteroatom-containing moiety (*Entry 6*), can be accommodated at the enal γ-position without affecting either the site-selectivity or the enantioselectivity of the vinylogous S_N1-type process (*Entries 1–6*). Remarkably, γ-aryl-substituted enals are competent substrates for this catalytic system (*Entries 7–9*). For these substrates, the γ-alkylation protocol opens a direct access to enantiomerically enriched benzylic stereogenic center, a valuable stereochemical motif in medicinal chemistry due to its recurring presence among therapeutic agents. Different aliphatic substituents in the α-position of the enals are well-tolerated, enabling access to a broad variety of multifunctional molecules with complete γ-site-selectivity and moderate-to-high levels of enantioselectivity (*Entries 10* and *11*). As a limitation of the system, 2-phenylpent-2-enal, bearing a Ph group at the α-position, reacted smoothly providing the corresponding product **5l** with a modest level of stereocontrol (40% ee; *Entry 12*).

We also explored the possibility of extending chiral secondary-amine-induced vinylogous nucleophilicity to cyclic α-branched enals. The protocol developed for the linear substrates can be translated to cyclopent-1-ene-1-carboxaldehyde and cyclohex-

Table 5. *The Scope of the Secondary-Amine-Catalyzed Asymmetric γ-Alkylation of α-Branched Enals*[a])

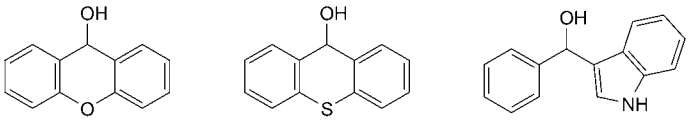


Entry	R^1	R^2	Product	*t* [h]	Yield [%][b])	ee [%][c])
1	Me	Me	**5a**	24	88	93
2	Me	Et	**5b**	32	74	96
3[d])	Me	^{i}Pr	**5c**	48	63	94
4	Me	Allyl	**5d**	50	82	94
5	Me	Bn	**5e**	43	59	95
6	Me	$MeSCH_2$	**5f**	48	40	90
7	Me	Ph	**5g**	6	92	92
8	Me	4-MeO–C_6H_4	**5h**	6	88	94
9	Me	4-Cl–C_6H_4	**5i**	5.5	92	91
10[d])	Et	Et	**5j**	78	82	92
11	Bn	Bn	**5k**	48	83	94
12	Ph	Me	**5l**	26	82	40

[a]) Reactions performed in toluene without any precaution for excluding air at 40° on a 0.1-mmol scale, with 20 mol-% of amine **1c**, 40 mol-% of saccharin, 4 equiv. of enal **3** with $[\mathbf{4a}]_0 = 0.25$M. ^{1}H-NMR Analysis of the crude mixture indicated a highly γ-site-selective alkylation pathway. [b]) Yield of the isolated product **5** after chromatographic purification on SiO_2. [c]) Determined by HPLC analysis on chiral stationary phases. [d]) Reaction carried out in toluene with $[\mathbf{4a}]_0 = 0.5$M.

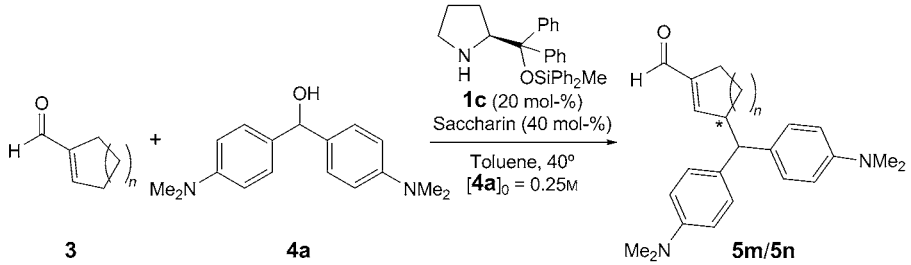
1-ene-1-carboxaldehyde, maintaining a good level of reactivity but with moderate stereoselectivity (*Table 6*). Notably, the five-membered substrate proved very reactive, the reaction reaching completion within 4 h (*Entry 1*).

To further delineate the reaction scope, we tested other alcohols able to generate stable carbocations through acid-catalyzed ionization. Xanthydrol (**6a**) and thioxanthydrol (**6b**) [13a] reacted smoothly under the reaction conditions, leading to the γ-alkylated products **7a** and **7b**, respectively, with synthetically meaningful results (*Table 7*, *Entries 1* and *2*). (1*H*-Indol-3-yl)(phenyl)methanol (**6c**) [13a][18a] can be used to easily access relevant indole-containing compounds in high ee, but with low control of the diastereoselection (*Entry 3*).



6a **6b** **6c**

Table 6. *The Asymmetric γ-Alkylation of Cyclic α-Branched Enals*[a])

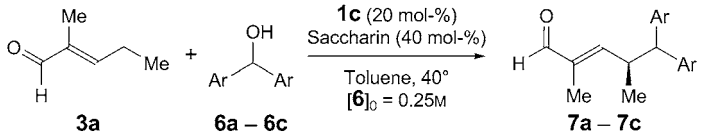


3 **4a** **5m/5n**

Entry	*n*	Product	*t* [h]	Yield [%][b])	ee [%][c])
1	1	**5m**	4	76	68
2	2	**5n**	32	86	63

[a]) Reactions performed in toluene without any precaution for excluding air at 40° on a 0.1-mmol scale, with 20 mol-% of amine **1c**, 40 mol-% of saccharin, 4 equiv. of enal **3** with $[\mathbf{4a}]_0 = 0.25$M. ^{1}H-NMR Analysis of the crude mixture indicated a highly γ-site-selective alkylation pathway. [b]) Yield of the isolated product **5** after chromatographic purification on silica gel. [c]) Determined by HPLC analysis on chiral stationary phases.

Table 7. *Carbocation Precursor Scope*[a])



3a **6a – 6c** **7a – 7c**

Entry	**6**	**7**	*t* [h]	Yield [%][b])	dr[c])	ee [%][d])
1[e])	**6a**	**7a**	30	65	–	81
2[f])	**6b**	**7b**	30	78	–	81
3	**6c**	**7c**	25	52[g])	1.3 : 1	87/92

[a]) Reactions performed in toluene without any precaution for excluding air at 40° on a 0.1-mmol scale, with 20 mol-% of amine **1c**, 40 mol-% of saccharin, 4 equiv. of enal **3** with $[\mathbf{6}]_0 = 0.25$M. ^{1}H-NMR Analysis of the crude mixture indicated a highly γ-site-selective alkylation pathway. [b]) Yield of the isolated product **7** after chromatographic purification on SiO_2. [c]) Determined by ^{1}H-NMR analysis of the crude mixture. [d]) Determined by HPLC analysis on chiral stationary phases. [e]) Reaction performed in MeCN with $[\mathbf{6}]_0 = 0.5$M; 2,4-NO_2–$C_6H_3CO_2H$ was used as the acidic additive. [f]) Reaction performed in MeCN with $[\mathbf{6}]_0 = 0.5$M. [g]) Yield of the product obtained as a mixture of diastereoisomers.

The absolute configuration of compound **7b** was unambiguously determined by anomalous-dispersion X-ray crystallographic analysis: an (*S*) absolute configuration at the newly formed γ-stereogenic center was inferred (*Fig. 1*).

Mechanistic Investigations. – We decided to carry out preliminary mechanistic investigations, by combining theoretical and spectroscopic approaches, to elucidate the mechanism of catalysis and to understand the origin of the stereoselectivity. We used NMR spectroscopic analyses to gain information on the conformational behavior of the

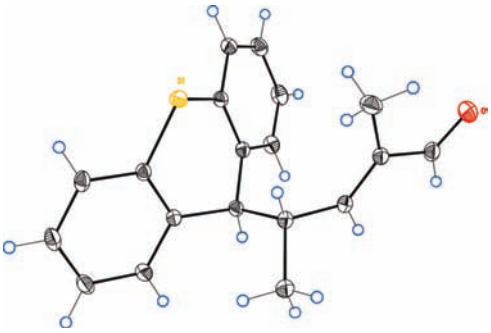
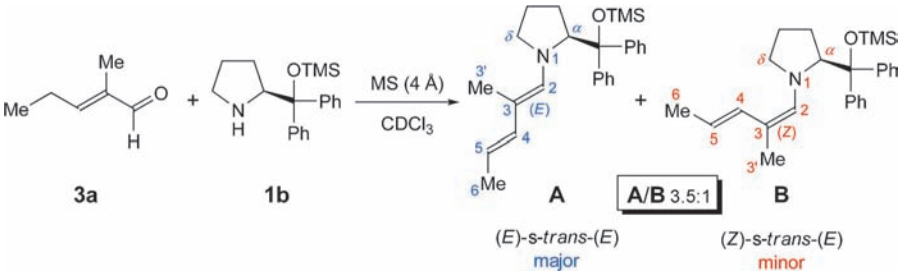


Fig. 1. *X-Ray structure of the product* **7b**. Crystallographic data are available free of charge from the *Cambridge Crystallographic Data Centre*, accession No. CCDC-894226.

covalent dienamine intermediate, which is actively involved in the configuration-determining step[16]). An intimate appreciation of the interactions that allow the amine catalyst to effectively control the molecular topology of the dienamine intermediate may provide fundamental clues to understand and rationalize the origin of the stereoselectivity. We investigated spectroscopically the dienamine intermediate generated by direct condensation of 2-methylpent-2-enal **3a** with the *Jørgensen–Hayashi* catalyst **1b**[17]), generated in the presence of 4-Å molecular sieves as detailed in the *Exper. Part*[18]).

In $CDCl_3$, two different isomers **A** and **B** (shown in *Scheme 2*) were found in 3.5:1 ratio of abundance. Their conformational behavior was investigated by conventional NMR techniques (*Fig. 2*), particularly vicinal coupling constant analysis and nuclear *Overhauser* enhancement (NOE) spectroscopy.

Scheme 2. *The Dienamine Intermediates Derived from Condensation of 2-Methylpent-2-enal* **3a** *and Amine* **1b**. MS, Molecular sieves.



[16]) For the characterization of covalent reactive intermediates involved in amine-catalytic processes, see [24].

[17]) The dienamine intermediate derived from the catalyst **1c** was too unstable for allowing an exhaustive NMR analysis. We assume that the dienamine studied in the spectroscopic investigations, derived from the parent amine **1b**, should be structurally similar to the one obtained from the bulkier catalyst **1c**.

[18]) For the characterization of covalent reactive intermediates formed by condensation of diarylprolinol silyl ether catalysts with aldehydes, see [25], and also [17a] and [26].

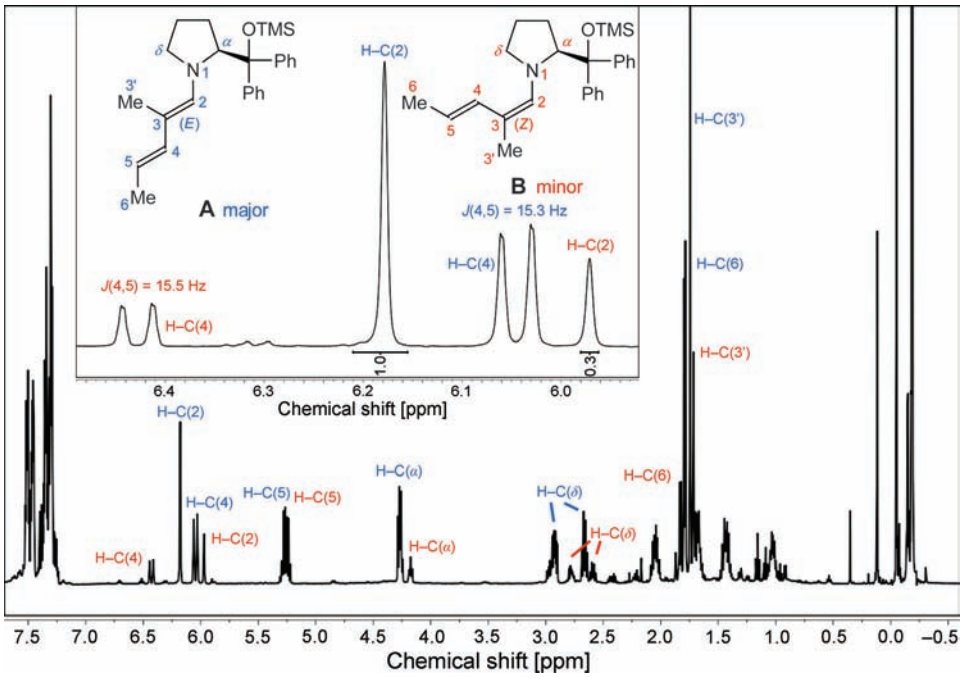


Fig. 2. *^{1}H-NMR of the crude from the condensation of amine* **1b** *and 2-methylpent-2-enal* **3a** *in $CDCl_3$ at 298 K. Inset:* the most diagnostic signals.

Several topological elements have the same geometry in the major and the minor isomers **A** and **B**, respectively. The presence of strong NOESY cross-peak between the H–C(2) and H–C(α) indicates a s-*trans*-conformation of the single bond connecting N(1)–C(2) (*Fig. 3*). Additionally, the 15.5- and 15.3-Hz coupling constants between H–C(4) and H–C(5) for the intermediates **A** and **B**, respectively, are evidence of an (*E*)-configured C(4)=C(5) bond. Finally, the NOE cross-peak between H–C(3′) and H–C(5) (H-atom signal overlap for the major and the minor species) suggests an s-*trans*-conformation around the C(3)–C(4) bond.

The two dienamine conformers differ in the configuration of the C(2)=C(3) bond. The major isomer **A** has an (*E*)-configured C=C bond, assigned on the basis of the two NOESY cross-peaks between H–C(3′) and H–C(δ), and H–C(4) and H–C(2) (*Fig. 3*). In contrast, the minor isomer **B** has a (*Z*)-configured C=C bond, as assigned on the basis of the two diagnostic NOESY signals H–C(3′)/H–C(2) and H–C(4)/H–C(δ). Overall, these studies establish the (*E*)-s-*trans*-(*E*) as the most populated ground-state conformation of the major isomer, while the minor isomer has a (*Z*)-s-*trans*-(*E*) topology.

We then carried out conformational studies in (D_8)toluene, the deuterated analog of the reaction medium. Two isomers, having the same topological arrangement as in $CDCl_3$, were detected. However, the major (*E*)-s-*trans*-(*E*) dienamine of type **A** was formed in a much higher relative abundance (**A**/**B** 10:1; *Figs. 4* and *5*).

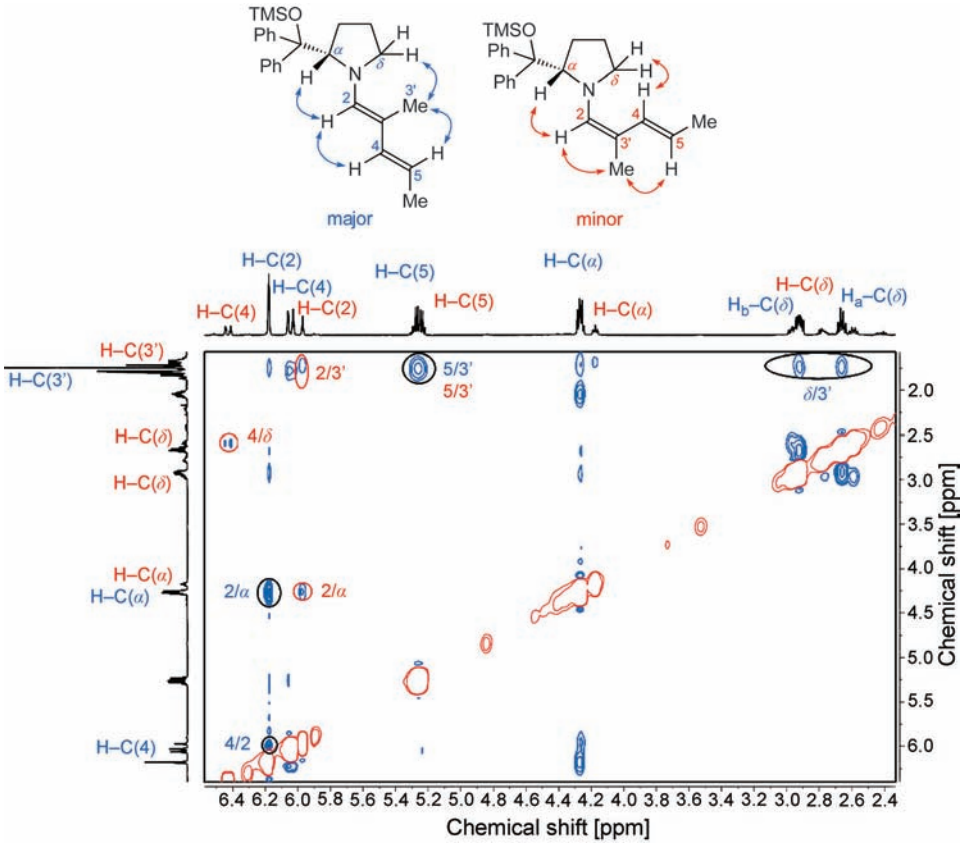


Fig. 3. *NOESY Spectra in $CDCl_3$ at 298 K*

These findings provoke interesting mechanistic considerations when compared with the spectroscopic studies carried out by *Jørgensen* and co-workers [8] on the dienamine adduct derived by condensation of a similar catalyst (amine **1a**) with a linear unsubstituted α,β-unsaturated aldehyde (see *Scheme 3*). For this system, two possible conformers were detected in a C_6D_6 solution, differing in the geometry of the second C=C bond, more distant from the N-atom. The major isomer showed a (*Z*)-configuration of this topological element.

Remarkably, both detected dienamines derived from the α-branched enal **3a** show an exclusive (*E*)-geometry at the remote C=C bond. There thus arises the interesting prospect that the α-branched enals, which are generally difficult substrates for enamine and iminium ion catalysis, have the structural properties (namely the α-substituent) to bias the dienamine geometry, a necessary requirement for forging a stereogenic center at the γ-position with high fidelity.

To gain more insights into the conformational preferences of the dienamine structures derived from α-branched enals, we performed a computational analysis by means of the hybrid functional B3LYP with the 6-31G(d) basis. This level of theory has

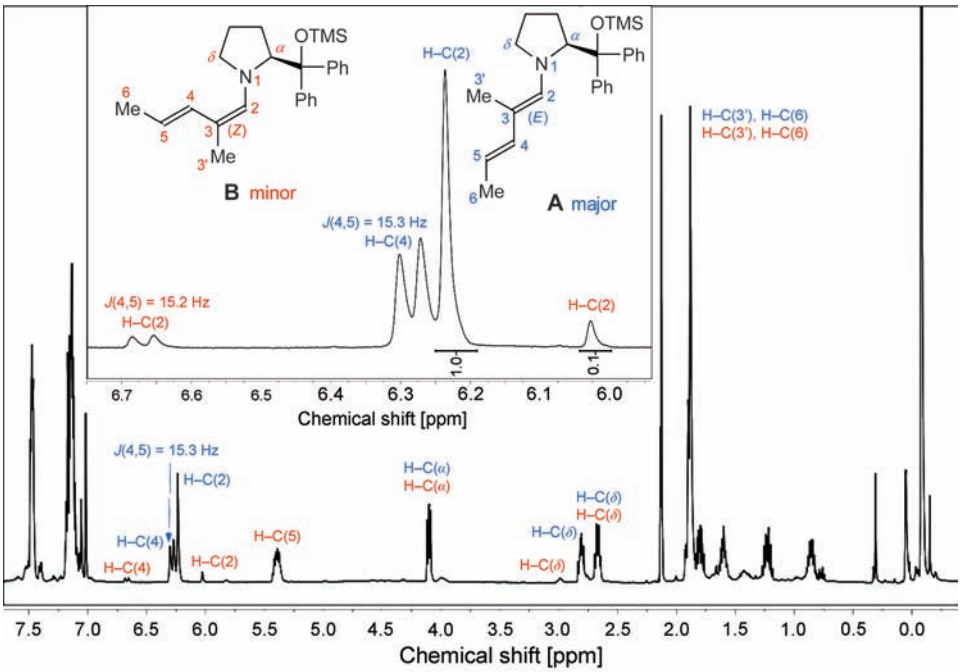


Fig. 4. *^{1}H-NMR of the crude from the condensation of amine* **1b** *and 2-methylpent-2-enal* **3a** *in (D_8)toluene at 298 K*

been previously used for accurate geometry optimizations of similar compounds [26]. Single-point energy calculations were performed with M06-2X/6-311++G(d,p) on B3LYP/6-31G(d) geometries to reproduce the dispersion effect [27]. *Fig. 6* shows the five energy minima found after optimization of several isomers of the dienamine.

The optimized geometries have relative energies in agreement with the spectroscopic results. This level of theory suggests that the (*E*)-s-*trans*-(*E*) dienamine of type **A** is the most stable isomer, as experimentally observed in solution. The minor (*Z*)-s-*trans*-(*E*) isomer **B** is by 0.4 kcal/mol less stable, a difference in energy which corresponds to a 2:1 ratio of **A** to **B** in the gas phase at 298 K. This ratio is similar to the 3.5:1 ratio spectroscopically observed in $CHCl_3$.

The other isomers are much higher in energy, but their analysis can provide interesting insights. Intermediate **C**, characterized by a s-*cis*-conformation around the N(1)–C(2) bond, is greatly destabilized by the steric clash between the methyl α-branched substituent and the diphenyl silyl ether fragment. Isomer **D**, with a s-*cis*-conformation of the C(3)–C(4) bond, is by 2.8 kcal/mol less stable than **A**, an energy penalty that somehow reflects the 2.4-kcal/mol difference reported between the s-*trans*/s-*cis* conformations of 2,4-dimethylbuta-1,3-diene [28]. Finally, the 1,3-allylic strain between the two Me groups greatly destabilizes the conformer **E**, having a (*Z*)-configured C(4)=C(5) bond. As previously commented (*Scheme 3*), the adduct **E** is the analog of the major conformer detected in solution for a dienamine derived from α-unsubtituted linear enals [8].

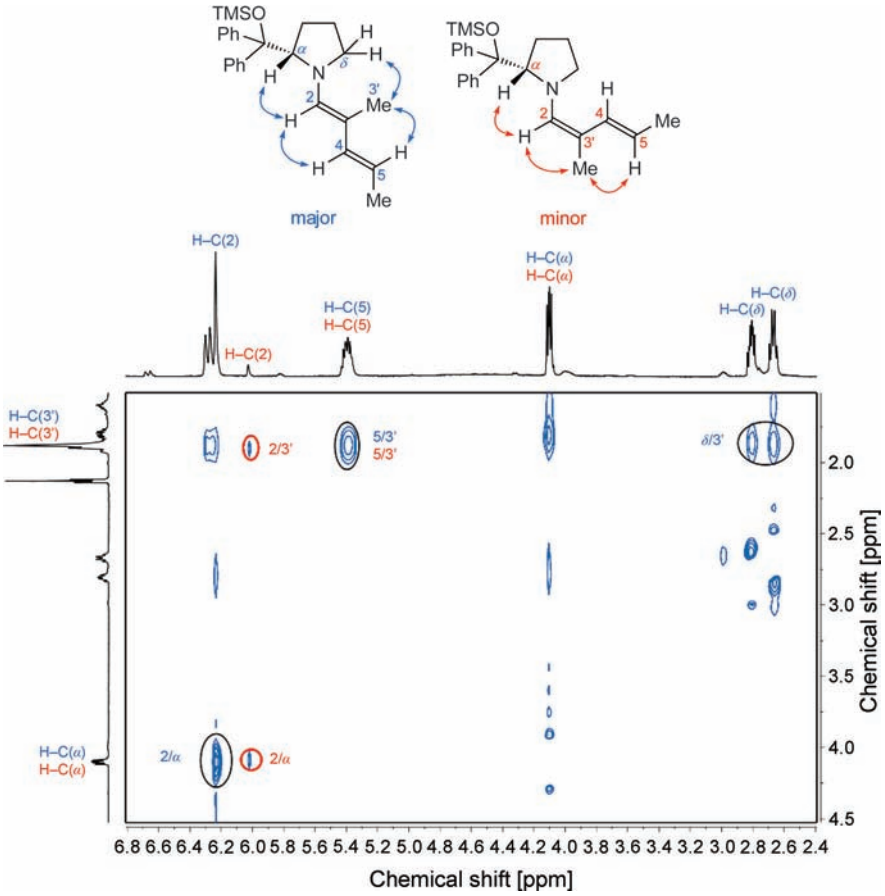


Fig. 5. *NOESY Spectra in (D_8)toluene at 298 K*

Our mechanistic studies have identified the (*E*)-s-*trans*-(*E*) isomer **A** as the thermodynamically more stable dienamine in solution. Based on these findings, we can propose a model for rationalizing the stereoselectivity of the γ-alkylation of α-branched enals. The classical 'steric control approach' [9c] generally invoked to rationalize the stereochemical outcome of a process catalyzed by the *Jørgensen–Hayashi*-type catalyst is consistent with the sense of asymmetric induction observed. Indeed, the efficient shielding by the chiral fragment in **1c** determines the selective engagement of the *in situ* generated carbocation with the *Si*-face of the more stable dienamine intermediate (*Fig. 7*)[19]).

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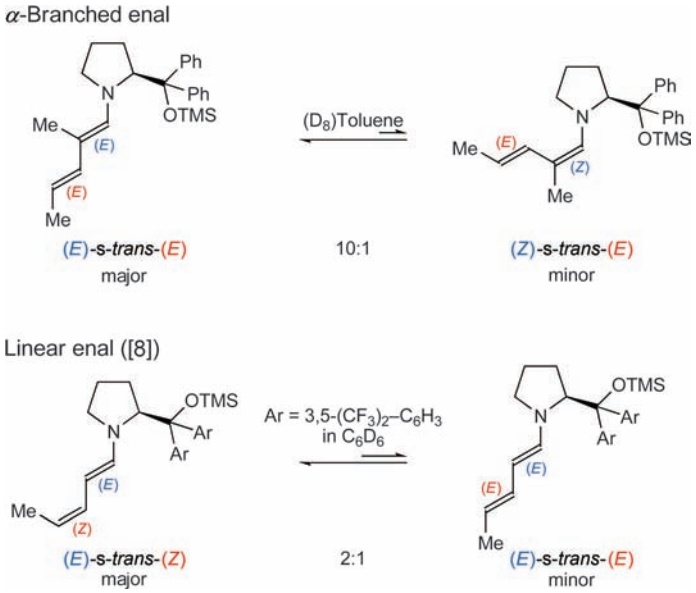
[19]) Another striking difference between α-branched and linear enals can be envisaged when considering the stereochemical outcome of the S_N1-type γ-alkylation chemistry catalyzed by the *Jørgensen–Hayashi*-type catalyst. Indeed, on the basis of the data reported by *Christmann* and co-workers [16], the sense of stereoinduction when using linear enals [16] and *a*-branched enals (this work), but the same catalyst enantiomer and alcohol **4a**, is opposite.

Scheme 3. *Comparison of the Conformational Behavior of the Dienamines Formed by Condensation of α-Branched and Linear Enals with Diaryl-prolinol Silyl Ether Derivatives*



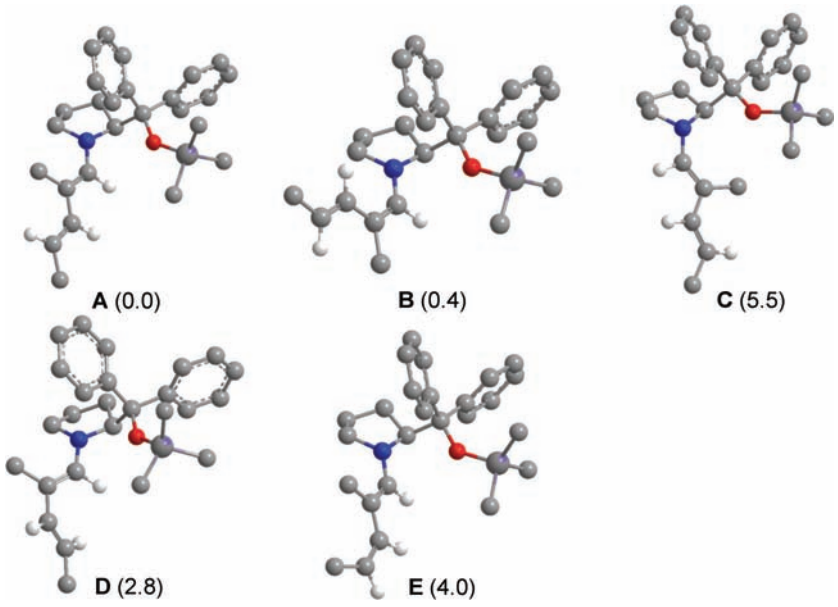


Fig. 6. *Optimized geometries and relative energies* (in kcal/mol in parenthesis) *at M06-2X/6-311++G(d,p)// B3LYP/6-31G(d) level of the more stable dienamine conformers*

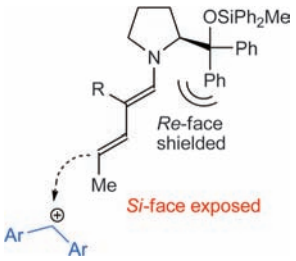


Fig. 7. *Stereochemical model for the γ-alkylation of α-branched enals catalyzed by (*S*)-diphenylpyrrolidine-2-methanol methyl(diphenyl)silyl ether* **1c**

Conclusions. – We have reported an effective catalytic system for the direct γ-site-selective alkylation of α-branched enals proceeding through an S_N1 pathway. Key to the development of the chemistry was the ability of chiral secondary-amine catalysis to activate α-substituted α,β-unsaturated aldehydes toward vinylogous nucleophilicity. We expect this unexpected reactivity will rapidly find application in the design of other asymmetric direct γ-functionalizations of sterically hindered CO compounds.

Research support from the *ICIQ Foundation*, *MICINN* (grant CTQ2010-15513), and the *European Research Council* (ERC Starting Grant ORGA-NAUT to *P. M.*) is gratefully acknowledged. *C. C.* and *A. M.* are grateful to *MICINN* for a FPI predoctoral fellowship and a JdC postdoctoral fellowship, respectively. The authors thank *Elena Arceo* for her contribution, and *Eduardo Escudero-Adán* for X-ray crystallographic analysis.

Experimental Part

General. All the reactions were set up under air and using freshly dist. solvents, without any precautions to exclude moisture, unless otherwise noted. All the yields reported in the optimization studies are obtained through ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as the internal standard (3.75 (*s*, 3 MeO); 6.08 (*s*, 3 arom. H)) and comparing these signals with those of the aldehyde H-atom of the product **5a**. Chromatographic purification of products was accomplished by force-flow chromatography (FC) on silica gel (SiO_2; 35–70 mesh). For TLC analysis, *Merck* precoated TLC plates (silica gel *60 GF$_{254}$*, 0.25 mm) were used, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aq. $KMnO_4$, and heat as developing agents. HPLC Analysis on chiral stationary phase was performed on an *Agilent 1200* series instrumentation. *Daicel Chiralpak IA*, *IC*, *IA-3*, or *IC-3* columns with ^{i}PrOH/hexane as the eluent were used. HPLC Traces were compared to racemic samples prepared by performing the reactions in the presence of a catalytic amount of an equimolar mixture of (*R*)- and (*S*)-diphenylprolinol trimethylsilyl ether **1b**. Optical rotations are reported as $[\alpha]_D^{r.t.}$ (*c* in g/100 ml, solvent). The ^{1}H- and ^{13}C-NMR spectra were recorded at 400 or 500 MHz for ^{1}H, and at 100 and 125 MHz for ^{13}C; the chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$ at 7.26 (^{1}H-NMR) and 77.0 ppm (^{13}C-NMR)); coupling constants, *J*, are given in Hz. C-Atom types were determined from DEPT ^{13}C-NMR experiments. High-resolution mass spectra (HR-MS): ICIQ unit on *LCT-Premier* time-of-flight (TOF) mass spectrometer by direct infusion with ESI. X-Ray data were obtained from the ICIQ X-Ray unit using a *Bruker-Nonius* diffractometer equipped with an *APPEX 2 4K CCD* area detector.

Catalysts **1a** and **1b** are commercially available. Catalyst **1c** was prepared starting from commercially available (*S*)-α,α-diphenylprolinol according to the procedure described in [17a]. The aldehydes **3** were purchased from commercial suppliers and used without further purification; otherwise, they were synthesized according to the procedure described in [15]. Aldehyde **3k** has been obtained from

autocondensation of hydrocinnamaldehyde following the procedure reported by *Erkkilä* and *Pihko* [29]. *Bis[4-(dimethylamino)phenyl]methanol* (**4a**) and *xanthydrol* (=*9*H-*xanthen-9-ol*; **4b**) are commercially available. *(1*H-*Indol-2-yl)(phenyl)methanol* (**4d**) [30] and *thioxanthydrol* (=*9*H-*thioxanthen-9-ol*; **4c**) were synthesized according to known procedures [31].

General Procedure (*GP*) *for the γ-Alkylation of α-Branched Enals.* All the reactions were carried out in toluene (synthesis grade, > 99%) without any precaution for excluding air and moisture. An ordinary 1-ml vial equipped with a *Teflon*-coated stir bar and a plastic screw cap was charged with 0.1 mmol of the alcohol **4**, 0.02 mmol of (−)-(*S*)-*α*,*α*-diphenylpyrrolidine-2-methanol methyl(diphenyl)silyl ether (**1c**) and 0.4 mmol of the enal **3** in 400 µl of toluene ($[\mathbf{4}]_0 = 0.25$M). Then, 0.04 mmol of saccharin was added. The vial was sealed and immerged in a H_2O bath (thermostated at 40°), and stirring was continued for the time specified in the *Tables*. The mixture assumes a green color that disappears upon complete consumption of the alcohol **4** (generally 24–36 h). Upon completion of the reaction (as verified by TLC), the mixture is directly charged on SiO_2 and subjected to chromatographic purification with hexane/Et_2O or toluene/Et_2O. All the products are stable if conserved in sealed vials flushed with Ar and stored at 0° in the absence of any trace of acids (for spectroscopic analysis, basified $CHCl_3$ pre-treated with K_2CO_3 was employed).

Known and previously unreported compounds were fully characterized. The absolute configuration of the *γ*-alkylated products **5** was assigned by comparison of the optical rotation to those of known compounds [15], while the absolute configuration for compound **7b** was unambiguously determined by anomalous-dispersion X-ray crystallographic analysis[20]).

*(2*E*,4*S*)-5,5-Bis[4-(dimethylamino)phenyl]-2,4-dimethylpent-2-enal* (**5a**). The reaction was carried out according to *GP*. After 24 h, the title compound was isolated by FC (eluent hexane/Et_2O 4:1) as a colorless oil (31 mg, 0.088 mmol, 88%). ee 93% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 95:5; flow rate, 1.00 ml/min, *λ* 254 nm: t_R(major), 8.4, t_R(minor), 9.6 min). $[\alpha]_D^{26} = +30.4$ ($c = 0.73$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.24 (*s*, 1 H); 7.17–7.10 (*m*, 2 H); 7.07–7.00 (*m*, 2 H); 6.72–6.63 (*m*, 2 H); 6.61–6.54 (*m*, 2 H); 6.32 (*dq*, *J* = 9.9, 1.4, 1 H); 3.62 (*d*, *J* = 10.5, 1 H); 3.50–3.40 (*m*, 1 H); 2.86 (*s*, 6 H); 2.90 (*s*, 6 H); 1.74 (*d*, *J* = 1.4, 3 H); 1.01 (*d*, *J* = 6.6, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.6; 160.1; 149.1; 149.0; 137.6; 132.1; 132.0; 128.6; 128.3; 112.8; 112.6; 56.2; 40.7; 40.6; 38.2; 19.0; 9.3.

*(2*E*,4*S*)-4-{Bis[4-(dimethylamino)phenyl]methyl}-2-methylhex-2-enal* (**5b**). The reaction was carried out according to *GP*. After 32 h, **5b** was isolated by FC (eluent hexane/Et_2O 5:1) as a white solid (27 mg, 0.074 mmol, 74%). ee 96% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 95:5; flow rate, 1.00 ml/min; *λ* 254 nm: t_R(major) 8.4 min, t_R(minor) 9.5 min). $[\alpha]_D^{25} = +7.1$ ($c = 1.24$, $CHCl_3$, 96% ee). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.27 (*s*, 1 H); 7.20–7.11 (*m*, 2 H); 7.09–6.92 (*m*, 2 H); 6.76–6.63 (*m*, 2 H); 6.63–6.52 (*m*, 2 H); 6.23 (*dq*, *J* = 10.3, 1.3, 1 H); 3.69 (*d*, *J* = 10.3, 1 H); 3.30 (*qd*, *J* = 10.3, 3.2, 1 H); 2.90 (*s*, 6 H); 2.85 (*s*, 6 H); 1.74 (*d*, *J* = 1.3, 3 H); 1.71–1.65 (*m*, 1 H); 1.26–1.20 (*m*, 1 H); 0.80 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.5; 158.9; 149.1; 148.9; 139.4; 132.1; 132.1; 128.5; 128.3; 112.8; 112.6; 54.8; 45.3; 40.7; 40.6; 26.5; 11.5; 9.9. HR-MS: 365.2596 ($[M+H]^+$, $C_{24}H_{33}ON_2^+$; calc. 365.2593).

*(2*E*,4*S*)-4-{Bis[4-(dimethylamino)phenyl]methyl}-2,5-dimethylhex-2-enal* (**5c**). The reaction was carried out according to *GP*, but with $[\mathbf{4a}]_0 = 0.5$M. After 48 h, **5c** was isolated by FC (eluent hexane/Et_2O 4:1) as a white solid (24 mg, 0.063 mmol, 63%). ee 94% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 80:20; flow rate, 1.00 ml/min; *λ* 254 nm: t_R(major) 4.7, t_R(minor) 5.8 min). $[\alpha]_D^{26} = -12.5$ ($c = 0.70$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.25 (*s*, 1 H); 7.22–7.15 (*m*, 2 H); 7.06–7.00 (*m*, 2 H); 6.70–6.66 (*m*, 2 H); 6.55–6.51 (*m*, 2 H); 6.30 (*dq*, *J* = 11.1, 1.3, 1 H); 3.85 (*d*, *J* = 11.1, 1 H); 3.38 (*td*, *J* = 11.1, 3.1, 1 H); 2.90 (*s*, 6 H); 2.84 (*s*, 6 H); 1.92 (*sept.d*, *J* = 7.0, 3.1, 1 H); 1.71 (*d*, *J* = 1.3, 3 H); 0.89 (*d*, *J* = 7.0, 3 H); 0.83 (*d*, *J* = 7.0, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.5; 156.2; 149.1; 148.9; 140.5; 132.3; 132.0; 128.3; 128.1; 112.9; 112.6; 52.7; 48.6; 40.7; 40.6; 29.8; 22.1; 15.7; 10.1.

*(2*E*,4*S*)-4-{Bis[4-(dimethylamino)phenyl]methyl}-2-methylhepta-2,6-dienal* (**5d**). The reaction was carried out according to *GP*. After 50 h, **5d** was isolated by FC (hexane/Et_2O 4:1 to 3:1) as a white solid (31 mg, 0.082 mmol, 82%). ee 94% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 94:6; flow rate, 1.00 ml/min; *λ* 254 nm: t_R(major) 8.2, t_R(minor) 8.9 min). $[\alpha]_D^{27} = -12.9$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR

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[20]) CCDC-894226 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

(500 MHz, $CDCl_3$): 9.26 (*s*, 1 H); 7.21 – 7.13 (*m*, 2 H); 7.08 – 6.99 (*m*, 2 H); 6.73 – 6.66 (*m*, 2 H); 6.61 – 6.53 (*m*, 2 H); 6.25 (*dq*, *J* = 10.4, 1.3, 1 H); 5.66 (*ddt*, *J* = 17.3, 10.2, 7.2, 1 H); 5.00 – 4.89 (*m*, 2 H); 3.74 (*d*, *J* = 10.4, 1 H); 3.55 – 3.41 (*m*, 1 H); 2.91 (*s*, 6 H); 2.85 (*s*, 6 H); 2.42 – 2.32 (*m*, 1 H); 2.10 – 1.98 (*m*, 1 H); 1.70 (*d*, *J* = 1.3, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.4; 158.0; 149.2; 149.0; 139.2; 135.4; 131.7 (×2); 128.6; 128.3; 116.8; 112.9; 112.6; 54.4; 43.6; 40.7; 40.6; 37.8; 9.9.

*(2*E*,4*S*)-4-Benzyl-5,5-bis[4-(dimethylamino)phenyl]-2-methylpent-2-enal* (**5e**). The reaction was carried out according to *GP*. After 43 h, **5e** was isolated by FC (eluent hexane/Et_2O 4 : 1) as a white solid (25 mg, 0.059 mmol, 59%). ee 95% (by HPLC, *Daicel Chiralpak IC*; hexane/^{i}PrOH 85 : 15; flow rate, 1.00 ml/min, λ 254 nm: t_R(major) 19.4 min, t_R(minor) 21.0 min). $[\alpha]_D^{26} = +5.2$ (*c* = 0.94, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.20 (*s*, 1 H); 7.29 – 7.21 (*m*, 2 H); 7.21 – 7.09 (*m*, 3 H); 7.07 – 6.96 (*m*, 4 H); 6.77 – 6.71 (*m*, 2 H); 6.61 – 6.52 (*m*, 2 H); 6.22 (*dq*, *J* = 10.3, 1.3, 1 H); 3.79 (*d*, *J* = 10.3, 1 H); 3.63 (*qd*, *J* = 10.3, 3.2, 1 H); 3.02 (*dd*, *J* = 13.4, 3.2, 1 H); 2.93 (*s*, 6 H); 2.85 (*s*, 6 H); 2.42 (*dd*, *J* = 13.4, 10.3, 1 H); 1.19 (*d*, *J* = 1.3, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.3; 157.3; 149.2; 149.0; 139.8; 139.6; 131.8; 131.7; 129.1; 128.6; 128.2; 128.1; 126.0; 113.1; 112.6; 54.9; 46.4; 40.7; 40.6; 39.8; 9.1.

*(2*E*,4*S*)-5,5-Bis[4-(dimethylamino)phenyl]-2-methyl-4-[(methylsulfanyl)methyl]pent-2-enal* (**5f**). The reaction was carried out according to *GP*. After 48 h, **5f** was isolated by FC (hexane/Et_2O 5 : 1 – 4 : 1) as a yellowish solid (16 mg, 0.040 mmol, 40%). ee 90% (by HPLC, *Daicel Chiralpak IA-3*; hexane/^{i}PrOH 97 : 3; flow rate, 0.80 ml/min; λ 254 nm: t_R(major) 14.0, t_R(minor) 15.0 min. $[\alpha]_D^{25} = +19.7$ (*c* = 1.07, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.29 (*s*, 1 H); 7.20 – 7.14 (*m*, 2 H); 7.06 – 7.01 (*m*, 2 H); 6.72 – 6.66 (*m*, 2 H); 6.61 – 6.54 (*m*, 2 H); 6.31 (*dq*, *J* = 10.3, 1.4, 1 H); 3.89 (*d*, *J* = 10.3, 1 H); 3.64 (*tdd*, *J* = 10.3, 8.7, 3.6, 1 H); 2.91 (*s*, 6 H); 2.86 (*s*, 6 H); 2.73 (*dd*, *J* = 12.8, 3.6, 1 H); 2.48 (*dd*, *J* = 12.8, 8.7, 1 H); 2.02 (*s*, 3 H); 1.74 (*d*, *J* = 1.4, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.3; 156.6; 149.2; 149.0; 140.1; 131.1 (2×); 128.5; 128.4; 113.0; 112.6; 53.9; 43.6; 40.7; 40.6; 38.6; 16.7; 10.0. HR-MS: 397.2333 ($[M+H]^+$, $C_{24}H_{33}N_2OS^+$; calc. 397.2314).

*(2*E*,4*S*)-5,5-Bis[4-(dimethylamino)phenyl]-2-methyl-4-phenylpent-2-enal* (**5g**). The reaction was carried out according to *GP*. After 6 h, **5g** was isolated by FC (hexane/Et_2O 4 : 1) as a white solid (38 mg, 0.092 mmol, 92%). ee 92% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 93 : 7; flow rate, 1.00 ml/min; λ 254 nm: t_R(major) 8.3, t_R(minor) 9.2 min). $[\alpha]_D^{26} = +6.9$ (*c* = 1.05, $CHCl_3$). ^{1}H-NMR (400 MHz $CDCl_3$): 9.25 (*s*, 1 H); 7.23 – 7.17 (*m*, 2 H); 7.17 – 7.09 (*m*, 5 H); 6.96 – 6.91 (*m*, 2 H); 6.65 – 6.59 (*m*, 3 H); 6.54 – 6.45 (*m*, 2 H); 4.50 (*t*, *J* = 10.9, 1 H); 4.26 (*d*, *J* = 10.9, 1 H); 2.89 (*s*, 6 H); 2.83 (*s*, 6 H); 1.70 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 195.3; 157.0; 149.1; 148.7; 141.7; 137.9; 131.2; 131.1; 128.7 (2×); 128.5; 128.3; 126.5; 112.6; 112.5; 55.4; 50.3; 40.6 (2×); 9.5.

*(2*E*,4*S*)-5,5-Bis[4-(dimethylamino)phenyl]-4-(4-methoxyphenyl)-2-methylpent-2-enal* (**5h**). The reaction was carried out according to *GP*. After 5.5 h, **5h** was isolated by FC (eluent hexane/Et_2O 2 : 1) as a white solid (39 mg, 0.088 mmol, 88%). ee 94% (by HPLC, *Daicel Chiralpak IC-3*; hexane/^{i}PrOH 80 : 20; flow rate, 0.80 ml/min; λ 254 nm: t_R(major) 25.9, t_R(minor) 30.8 min). $[\alpha]_D^{26} = -2.1$ (*c* = 1.00, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.25 (*s*, 1 H); 7.14 – 7.03 (*m*, 4 H); 6.99 – 6.92 (*m*, 2 H); 6.79 – 6.72 (*m*, 2 H); 6.66 – 6.57 (*m*, 3 H); 6.55 – 6.47 (*m*, 2 H); 4.47 (*dd*, *J* = 11.1, 9.9, 1 H); 4.21 (*d*, *J* = 11.1, 1 H); 3.74 (*s*, 3 H); 2.89 (*s*, 6 H); 2.83 (*s*, 6 H); 1.70 (*d*, *J* = 1.3, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.4; 158.0; 157.4; 149.1; 148.7; 137.6; 133.8; 131.4; 131.2; 129.2; 128.7 (2×); 113.9; 112.6; 112.5; 55.5; 55.1; 49.4; 40.6 (2×); 9.4.

*(2*E*,4*S*)-4-(4-Chlorophenyl)-5,5-bis[4-(dimethylamino)phenyl]-2-methylpent-2-enal* (**5i**). The reaction was carried out according to *GP*. After 6 h, **5i** was isolated by FC (hexane/Et_2O 3 : 1) as a white solid (41 mg, 0.092 mmol, 92%). ee 91% (by HPLC, *Daicel Chiralpak IA-3*; hexane/^{i}PrOH 90 : 10; flow rate, 0.80 ml/min; λ 254 nm: t_R(minor) 10.1, t_R(major) 10.9 min). $[\alpha]_D^{26} = +12.4$ (*c* = 1.00, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 9.25 (*s*, 1 H); 7.20 – 7.14 (*m*, 2 H); 7.12 – 7.03 (*m*, 4 H); 6.95 – 6.89 (*m*, 2 H); 6.64 – 6.55 (*m*, 3 H); 6.53 – 6.48 (*m*, 2 H); 4.47 (*dd*, *J* = 11.1, 9.7, 1 H); 4.18 (*d*, *J* = 11.1, 1 H); 2.89 (*s*, 6 H); 2.83 (*s*, 6 H); 1.67 (*d*, *J* = 1.3, 3 H). ^{13}C-NMR (100, MHz, $CDCl_3$): 195.1; 156.1; 149.2; 148.8; 140.4; 138.4; 132.1; 130.8; 130.7; 129.6; 128.7; 128.6; 128.6; 112.6; 112.5; 55.5; 49.7; 40.6 (2×); 9.5.

*(2*E*,4*S*)-4-{Bis[4-(dimethylamino)phenyl]methyl}-2-ethylhex-2-enal* (**5j**). The reaction was carried out according to *GP* but with $[\mathbf{4a}]_0 = 0.5$M. After 78 h, **5j** was isolated by FC (hexane/Et_2O 4 : 1) as a white solid (31 mg, 0.082 mmol, 82%). ee 92% (by HPLC, *Daicel Chiralpak IC*; hexane/^{i}PrOH 90 : 10; flow rate, 1.00 ml/min; λ 254 nm: t_R(major) 15.7, t_R(minor) 18.4 min). $[\alpha]_D^{27} = -16.7$ (*c* = 0.85, $CHCl_3$, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$): 9.23 (*s*, 1 H); 7.19 – 7.13 (*m*, 2 H); 7.06 – 7.00 (*m*, 2 H); 6.71 – 6.65 (*m*, 2 H);

6.59–6.53 (*m*, 2 H); 6.16 (*d*, *J* = 10.6, 1 H); 3.70 (*d*, *J* = 10.2, 1 H); 3.35–3.23 (*m*, 1 H); 2.90 (*s*, 6 H); 2.84 (*s*, 6 H); 2.22 (*q*, *J* = 7.5, 2 H); 1.73–1.62 (*m*, 1 H); 1.26–1.20 (*m*, 1 H); 0.91 (*t*, *J* = 7.5, 3 H); 0.80 (*t*, *J* = 7.5, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 195.6; 158.5; 149.1; 149.0; 144.9; 132.1; 131.8; 128.6; 128.4; 112.8; 112.6; 54.8; 45.0; 40.7; 40.7; 26.5; 18.2; 12.8; 11.6.

*(2*E*,4*S*)-2,4-Dibenzyl-5,5-bis[4-(dimethylamino)phenyl]pent-2-enal* (**5k**). The reaction was carried out according to *GP*. After 48 h, **5k** was isolated by FC (toluene/Et_2O 97:3 to 95:5) as a white solid (42 mg, 0.083 mmol, 83% yield). ee 94% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 96:4; flow rate. 1.00 ml/min; λ 254 nm: t_R(minor) 11.8, t_R(major) 12.5 min). $[\alpha]_D^{26} = -33.6$ (*c* = 1.00, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.29 (*s*, 1 H); 7.24–7.19 (*m*, 5 H); 7.15–7.12 (*m*, 3 H); 7.03–7.00 (*m*, 2 H); 6.88–6.82 (*m*, 2 H); 6.76–6.72 (*m*, 4 H); 6.49–6.44 (*m*, 2 H); 6.38 (*d*, *J* = 10.2, 1 H); 3.77 (*d*, *J* = 10.3, 1 H); 3.70–3.63 (*m*, 1 H); 3.12 (*d*, *J* = 15.1, 1 H); 3.01 (*dd*, *J* = 13.4, 3.2, 1 H); 2.93 (*s*, 6 H); 2.85 (*s*, 6 H); 2.69 (*d*, *J* = 15.1, 1 H); 2.46 (*dd*, *J* = 13.4, 9.4, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 194.8; 158.8; 149.2; 148.9; 142.3; 139.3; 138.8; 131.4; 131.4; 129.4; 128.7; 128.5; 128.5; 128.3; 128.1; 126.2; 125.7; 113.0; 112.6; 54.9; 46.4; 40.7; 40.6; 39.8; 29.3.

*(2*E*,4*S*)-5,5-Bis[4-(dimethylamino)phenyl]-4-methyl-2-phenylpent-2-enal* (**5l**). The reaction was carried out according to *GP*. After 26 h **5l** was isolated by FC (hexane/Et_2O 4:1) as a yellowish oil (34 mg, 0.082 mmol, 82%). ee 40% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 95:5; flow rate, 1.00 ml/min; λ 254 nm: t_R(major) 9.9, t_R(minor) 12.8 min). $[\alpha]_D^{25} = +38.9$ (*c* = 1.30, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 9.44 (*s*, 1 H); 7.48–7.39 (*m*, 3 H); 7.08–6.98 (*m*, 4 H); 6.92–6.87 (*m*, 2 H); 6.65–6.60 (*m*, 2 H); 6.59–6.51 (*m*, 3 H); 3.63 (*d*, *J* = 10.5, 1 H); 3.41–3.28 (*m*, 1 H); 2.88 (*s*, 6 H); 2.87 (*s*, 6 H); 1.07 (*d*, *J* = 6.5, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 193.9; 161.4; 149.1 (2×); 142.8; 133.1; 132.0; 131.6; 129.3; 128.5 (×2); 128.2; 127.8; 112.8; 112.6; 56.5; 40.7 (2×); 38.5; 19.7.

3-[Bis[4-(dimethylamino)phenyl]methyl]cyclopent-1-ene-1-carbaldehyde (**5m**). The reaction was carried out according to *GP*. After 4 h, **5m** was isolated by FC (toluene/Et_2O from 96:4 to 95:5) as a yellowish oil (26 mg, 0.076 mmol, 76%). ee 68% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 90:10; flow rate, 1.00 ml/min, λ 254 nm: t_R(major) 11.2, t_R(minor) 12.2 min). $[\alpha]_D^{27} = +76.2$ (*c* = 1.00, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.69 (*s*, 1 H); 7.18–7.10 (*m*, 4 H); 6.72–6.64 (*m*, 5 H); 3.77–3.68 (*m*, 1 H); 3.60 (*d*, *J* = 11.2, 1 H); 2.91 (*s*, 6 H); 2.90 (*s*, 6 H); 2.62–2.51 (*m*, 1 H); 2.50–2.40 (*m*, 1 H); 2.17–2.06 (*m*, 1 H); 1.71–1.60 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 190.4; 156.3; 149.1; 149.1; 147.0; 132.6; 132.1; 128.4; 128.3; 112.9; 112.8; 55.0; 51.8; 40.7; 29.3; 27.8. HR-MS: 349.2263 ($[M+H]^+$, $C_{23}H_{28}N_2O^+$; calc. 349.2280).

3-[Bis[4-(dimethylamino)phenyl]methyl}cyclohex-1-ene-1-carbaldehyde (**5n**). The reaction was carried out according to *GP*. After 32 h, **5n** was isolated by FC (toluene/Et_2O 5:1) as a yellowish solid (31 mg, 0.086 mmol, 86%). ee 63% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 90:10; flow rate, 1.00 ml/min; λ 254 nm: t_R(major) 8.5, t_R(minor) 9.9 min). $[\alpha]_D^{26} = +8.7$ (*c* = 1.00, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.28 (*s*, 1 H); 7.20–7.11 (*m*, 4 H); 6.73–6.65 (*m*, 4 H); 6.65–6.61 (*m*, 1 H); 3.56 (*d*, *J* = 11.2, 1 H); 3.20–3.09 (*m*, 1 H); 2.92 (*s*, 6 H); 2.90 (*s*, 6 H); 2.33–2.25 (*m*, 1 H); 2.11–2.03 (*m*, 1 H); 1.87–1.76 (*m*, 1 H); 1.77–1.70 (*m*, 1 H); 1.56–1.47 (*m*, 1 H); 1.27–1.19 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 194.9; 154.6; 149.1; 149.1; 141.5; 132.0; 131.4; 128.6; 128.3; 113.0; 112.9; 54.9; 41.0; 40.7; 40.7; 28.0; 21.7; 20.6.

*(2*E*,4*S*)-2-Methyl-4-(9*H*-xanthen-9-yl)pent-2-enal* (**7a**). The reaction was carried out according to *GP*, but with $[\mathbf{6a}]_0 = 0.5$M and 2,4-dinitrobenzoic acid as the acidic additive (40% mol) in MeCN. After 30 h, the mixture was subjected to FC (hexane/Et_2O 95:5) to afford a mixture of the product and xanthone (this compound shows fluorescence at 354 nm). This mixture was finally purified on prep. TLC (CH_2Cl_2; R_f(product) 0.6) to afford **7a** as a white solid (18 mg, 0.065 mmol, 65%). ee 81% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 95:5; flow rate, 1.00 ml/min; λ 254 nm: t_R(minor) 5.6, t_R(major) 5.8 min). $[\alpha]_D^{26} = +13.8$ (*c* = 1.00, $CHCl_3$, 81% ee). HR-MS: 301.1210 ($[M+Na]^+$, $C_{19}H_{18}NaO_2^+$; calc. 301.1204). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.30 (*s*, 1 H); 7.29–7.22 (*m*, 2 H); 7.22–7.14 (*m*, 2 H); 7.13–7.04 (*m*, 4 H); 6.11 (*dq*, *J* = 10.3, 1.4, 1 H); 3.98 (*d*, *J* = 5.0, 1 H); 3.00 (*dqd*, *J* = 10.3, 6.8, 5.0, 1 H); 1.36 (*d*, *J* = 1.4, 3 H); 1.03 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.2; 155.8; 153.0; 152.9; 139.4; 129.2; 129.0; 128.1; 123.3; 123.2; 123.0; 122.7; 116.5; 116.4; 45.0; 42.4; 16.7; 8.8.

*(2*E*,4*S*)-2-Methyl-4-(9*H*-thioxanthen-9-yl)pent-2-enal* (**7b**). The reaction was carried out according to *GP*, but with $[\mathbf{6b}]_0 = 0.5$M and MeCN as the solvent. After 30 h, **7b** was isolated by FC (hexane/Et_2O

10:1) as a white solid (23 mg, 0.078 mmol, 78%). ee 81% (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 90:10; flow rate, 1.00 ml/min; λ 254 nm: t_R(minor) 6.2, t_R(major) 8.4 min). $[\alpha]_D^{26} = -106.7$ ($c = 0.85$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.31 (*s*, 1 H); 7.54–7.45 (*m*, 1 H); 7.44–7.33 (*m*, 1 H); 7.35–7.24 (*m*, 3 H); 7.21–7.03 (*m*, 3 H); 6.28 (*dq*, $J = 10.5, 1.3, 1$ H); 3.84 (*d*, $J = 9.8, 1$ H); 3.52–3.37 (*m*, 1 H); 1.18 (*d*, $J = 1.3, 3$ H); 0.94 (*d*, $J = 6.6, 3$ H). ^{13}C-NMR (125 MHz, $CDCl_3$): 195.2; 157.1; 139.7; 136.2; 135.7; 132.7; 132.5; 130.3; 129.8; 127.2; 126.9; 126.8; 126.7; 126.2; 126.0; 55.0; 33.2; 18.6; 8.5. HR-MS: 317.0961 ($[M + Na]^+$, $C_{19}H_{18}NaOS^+$; calc. 317.0976).

*(2*E*)-5-(1*H*-Indol-3-yl)-2,4-dimethyl-5-phenylpent-2-enal* (**7c**). The reaction was carried out according to *GP*. After 25 h, **7c** was isolated by FC (toluene/Et_2O 98:2 to 95:5) as a white solid (16 mg, 0.052 mmol, 52%) as a mixture of diastereoisomers in a ratio of 1.3:1 (checked by ^{1}H-NMR on the crude mixture) with an ee of 87 and 92%, resp. (by HPLC, *Daicel Chiralpak IA*; hexane/^{i}PrOH 80:20; flow rate, 1.00 ml/min; λ 254 nm: major diastereoisomer, t_R(minor) 6.5 min, t_R(major) 14.5 min; minor diastereoisomer, t_R(minor) 5.7 min, t_R(major) 7.5 min). ^{1}H-NMR (400 MHz, C_6D_6): 9.17 (*s*, 1 H); 7.63 (*d*, $J = 7.6, 1$ H); 7.23–6.89 (*m*, 10 H); 6.59–6.50 (*m*, 1 H); 6.01 (*d*, $J = 9.9, 1$ H); 3.98 (*d*, $J = 9.0, 1$ H); 3.41–3.31 (*m*, 1 H); 1.62 (*d*, $J = 1.4, 3$ H); 0.92 (*d*, $J = 6.7, 3$ H). ^{13}C-NMR (100 MHz, C_6D_6): 195.1; 158.5; 144.4; 139.2; 138.7; 137.4; 129.4; 129.2; 127.4; 123.2; 122.2; 120.6; 120.4; 118.9; 112.3; 49.8; 39.5; 19.9; 10.2. HR-MS: 326.1522 ($[M + Na]^+$, $C_{21}H_{21}NNaO^+$; calc. 326.1521).

Procedure for Preparing the Dienamine Intermediate. The reaction was conducted under Ar using *Schlenk* technique. *2-Methylpent-2-enal* (**3a**; 19.6 mg, 0.2 mmol) was added to a dry deuterated solvent (200 µl) containing freshly activated molecular sieves. (*S*)-α,α-Diphenylpyrrolidine-2-methanol trimethylsilyl ether (65 mg, 0.2 mmol, 1M) was added, and the mixture was stirred over 16 h at ambient temp. Then, the mixture was filtered under Ar through a 0.2-µm PTFE filter directly into a dry NMR tube. After dilution (until *ca.* 0.1–0.2M) with the same deuterated solvent (previously anhydrified on activated molecular sieves in pellets), the sample was analyzed by NMR spectroscopy (500 MHz).

Theoretical Calculations of Structures. The different structures of the dienamine intermediate were fully optimized at the B3LYP/6-31G(d) level [32]. For each structure, a frequency calculation has been performed to verify that it is an energy minimum, *i.e.*, having no imaginary frequency. Energy evaluations of the B3LYP/6-31G(d)-optimized structures were carried out at the M06-2X [33] levels using a larger basis set, 6-311++G(d,p) [34]. The B3LYP calculations do not reproduce dispersion effects, but the M06–2X calculations do consider them, at least in part [27]. The Gaussian 09 program [35] was used for all theoretical calculations.

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