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Enantioselective α- and γ-Alkylation of α,β-Unsaturated Aldehydes Using Dienamine Activation

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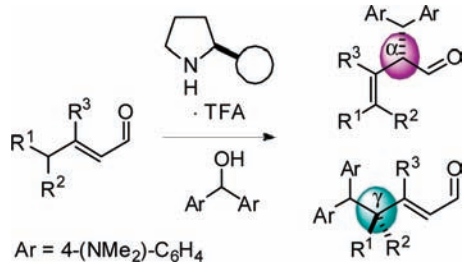
ABSTRACT



The enantioselective alkylation of α,β-unsaturated aldehydes with stabilized carbocations as electrophiles via the activation as dienamine intermediates is described. This unique application of dienamine catalysis allows for the first enantioselective γ-alkylation of linear α,β-unsubstituted enals.

The design of novel synthetic methods for the rapid and stereoselective functionalization of complex molecular scaffolds remains a key challenge in organic synthesis.[1] Over the past decade, organocatalysis[2] has emerged as a complementary alternative to metal-catalyzed transformations. In particular, enamine-,[3] iminium-,[4] and SOMO-catalysis[5] have vastly added to the synthetic utility and versatility of carbonyl compounds. Following Yamada's[6] stoichiometric asymmetric alkylation of proline derived dienamines in the 1970s, catalytic dienamine activation[7] has recently developed as a powerful extension of enamine catalysis. For a full exploitation of this activation mode, a comprehensive understanding

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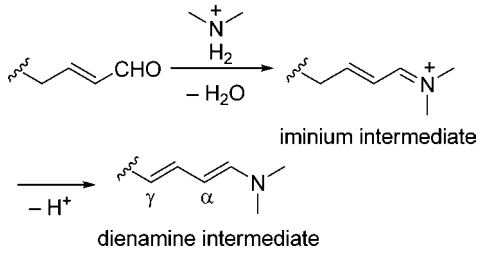
of the associated chemo-, regio-, and stereoselectivity and their substrate dependence is required. Dienamines are readily formed by condensation of amines with α,β-unsaturated carbonyl compounds via iminium intermediates followed by deprotonation in the γ-position (Scheme 1). The vinylogy

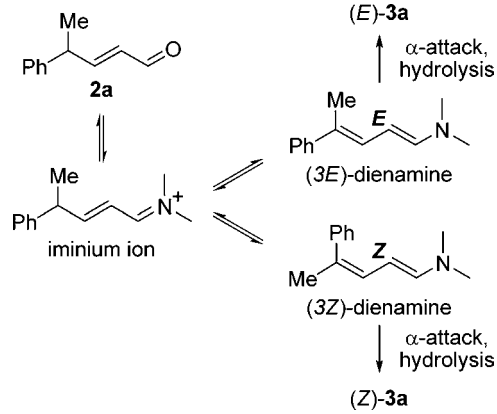
Scheme 1. Formation of Dienamine Intermediates



principle[8] dictates bidentate reactivity by transmission of nucleophilic behavior through the conjugated π-system. Accordingly, dienamine intermediates can be trapped by suitable electrophiles E^+ in the α- and γ-position. In addition, dienamines have been employed as an electron-rich diene component in regular Diels−Alder-type reactions[9] as well as a dienophile in aza-Diels−Alder reactions with an inverse electron demand.[10]

In previously reported reactions via dienamine intermediates, high regioselectivity often required the use of substituted homologues in order to shut down competing pathways. For example, γ-disubstituted aldehydes were used by Chen in selective α-alkylations with nitrostyrenes.[11] Recently, Melchiorre employed 3-methylcyclohexenones in γ-substitutions with nitrostyrenes.[12] In our previous work on Rauhut−Currier-type reactions,[13] β-disubstitution was essential for high reactivity and selectivity. In order to probe the general ambident reactivity of dienamine intermediates, we decided to study their alkylation with stabilized cations derived from bis[4-(dimethylamino)phenyl]methanol (**1**).[14,15] The enamine version of this enantioselective S_N1-type alkylation[16,17] reaction has been pioneered by Cozzi.[18,19] As a starting substrate, we chose (*E*)-4-phenylpent-2-enal (**2a**) because the phenyl group is capable of disfavoring the γ-substitution pathways sterically and electronically[11] (Scheme 2). In the

Scheme 2. Rationale for the Observed Products in the α-Selective Alkylation of **2a**



screening of diarylprolinol-derived catalysts with TFA as a cocatalyst, only **VI**, **VII**, and **X** were effective in both reactivity and enantioselectivity affording an *E*/*Z* mixture of **3a**[20] in ratios up to 6:1 (Table 1). Interestingly, less hindered catalysts **II**−**V** (entries 2−5) gave better *E*/*Z* ratios at the cost of lowered enantioselectivity.[21] Condensation of **2a** with the amine catalyst affords two interconverting diastereomeric dienamines, as evidenced by NMR spectroscopy. The *E*/*Z* ratio of the α-alkylation products results directly from the ratio of the diastereomeric dienamines coupled with their respective rates of alkylation (Scheme 2).[21]

As a key factor in dienamine equilibration and carbocation formation, we screened several organic acids as an additive as well as different solvents (Table 2). Surprisingly, no

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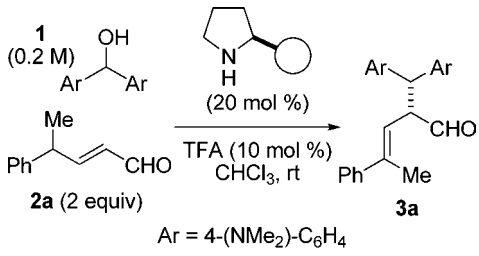
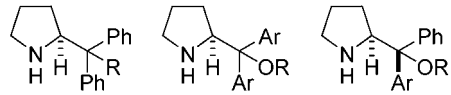
(20) The absolute configuration of (*E*)-**3a** was shown to be *R* by X-ray crystallography. See Supporting Information.

(21) NMR and computational studies probing the stability of the dienamine and its connection with the *E*/*Z* ratio in the final products will be reported in due course.

Table 1. α-Alkylation of α,β-Unsaturated Aldehydes: Catalyst Screening





I R = OH
II R = OTMS
III R = OTBS
IV R = Ph
V R = H
VI R = TMS
VII R = TBS
VIII R = H
IX R = TMS
X R = TBS

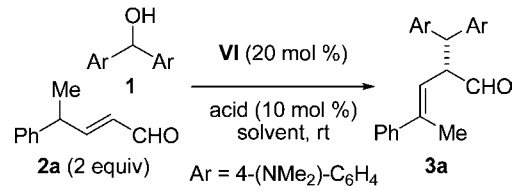
entry	catalyst	*t*[h]	yield[%][a]	*E*:*Z*[b]	*ee*[%][c]
1	**I**	5	50[d]	85:15	54 (17)
2	**II**	5	89[d]	90:10	33 (18)
3	**III**	8	80	87:13	28 (7)
4	**IV**	3	29[d]	90:10	−49 (28)
5	**V**	3	86[d]	93:7	42 (n.d.)[e]
6	**VI**	3	78	78:22	79 (49)
7	**VII**	4	96[d]	75:25	88 (72)
8	**VIII**	3	64	83:17	59 (47)
9	**IX**	3	81	88:12	61 (39)
10	**X**	3	91	86:14	81 (51)

[a] Yield of isolated product. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC for the major and the minor isomer (in parentheses). [d] Conversion by ^{1}H NMR. [e] Not determined.

obvious correlation between pK_a and selectivity was observed. Nevertheless, we were able to identify AcOH and toluene as useful alternatives to TFA and $CHCl_3$ (entries 1−4). As a general observation, AcOH provides better enantioselectivities, while TFA gives better *E*/*Z* ratios. Lowering the temperature to −20 °C (entries 10−11) with TFA as an acid additive resulted in good enantioselectivities (88−93% *ee*) with slightly better diastereoselectivities. On the other hand, no better results were obtained with catalyst **VII** (entries 12−14).

The optimized reaction conditions developed for the α-alkylation of **2a** were applied to a variety of differently substituted α,β-unsaturated aldehydes (Table 3). When the phenyl group was replaced by a methyl group (entry 1), the α-alkylated aldehyde **3b** was still a major regioisomer although in this instance significant amounts of γ-substituted product **4b** could be detected. This observation supports the idea of electronic destabilization of γ-substitution in **3a**, as it intercepts conjugation with the phenyl ring. Other disubstituted aldehydes (entries 2−4) gave similar results and α-alkylated aldehydes **3c**−**3e** in >92% *ee*. When linear α,β-unsaturated aldehydes were used (entries 5−7), γ-substitution became the dominating pathway affording aldehydes **4f**−**h** as the major products. The stereochemical outcome of the

Table 2. α-Alkylation of α,β-Unsaturated Aldehydes: Solvent and Acid Additive Screening



entry	solvent	acid	*t*[h]	yield[%][a]	*E*:*Z*[b]	*ee*[%][c]
1	$CHCl_3$	TFA	3	78	78:22	79 (49)
2	toluene	TFA	8	84	71:29	73 (77)
3	$CHCl_3$	AcOH	28	73	67:33	94 (93)
4	toluene	AcOH	20	78	66:34	94 (94)
5	Et_2O	AcOH	84	75	68:32	78 (80)
6	CH_2Cl_2	AcOH	20	84	69:31	89 (85)
7	CH_3CN	AcOH	52	85[d]	89:11	26 (n.d.)[e]
8	C_6F_6	AcOH	20	91[d]	83:17	87 (82)
9	xylene	AcOH	20	82[d]	69:31	93 (94)
10[f]	$CHCl_3$	TFA	96	86	80:20	88 (86)
11[f]	toluene	TFA	96	79	80:20	93 (92)
12[g]	$CHCl_3$	AcOH	37	60	69:31	90 (87)
13[f,g]	$CHCl_3$	TFA	96	92	78:22	92 (>99)
14[f,g]	toluene	TFA	96	64	75:25	89 (89)

[a] Yield of isolated product. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC for the major isomer (minor isomer in parentheses). [d] Conversion by ^{1}H NMR. [e] Not determined. [f] Reaction performed at −20 °C. [g] Catalyst **VII** was used.

γ-substitution was determined by X-ray crystallographic analysis of **4f** and **4g** (Figure 1).[22] Finally, when citral (**2i**) was used as a β-substituted α,β-unsaturated aldehyde (entry 8), the γ-alkylated product **4i** was formed exclusively, albeit as a 7:1 mixture of *E*/*Z* isomers. Not surprisingly, α-substituted aldehydes, notoriously unreactive toward secondary amine catalysts, did not yield any alkylation product.

In the case of linear aldehydes (Scheme 3), electrophilic attack of the ambident dienamine **I** occurs at the less encumbered γ-position leading to a mixture of (*E*)- and (*Z*)-iminium ions. Hydrolysis of the latter affords the α,β-unsaturated aldehydes **4f**. In iminium catalysis it was demonstrated that 2*E*- and 2*Z*-enals can interconvert in the presence of a secondary amines.[23] The required deprotonation/protonation sequence suggests the presence of the alkylated dienamine **II**. The *E*/*Z* ratio of the final products is dictated by thermodynamics, thereby explaining the lowered *E*-selectivity for **4i** (smaller energy difference). In contrast to the α-adduct **3**, there is no significant kinetic discrimination between the γ-substituted (**4**) and unreacted aldehyde (**2**); i.e. products **4** are substrates for the catalyst that could lead to dienamines **II**. This detail has ramifications for the stereochemical outcome of the γ-substitution. Even if double substitution can be suppressed, any intermediacy of γ-substituted

(22) See Supporting Information.

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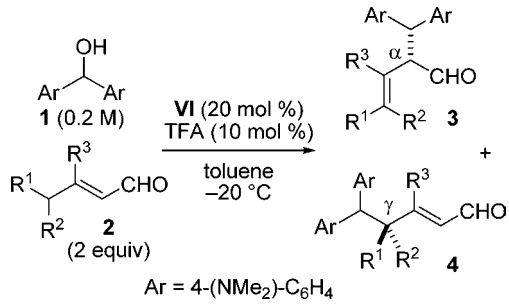
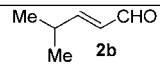
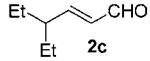
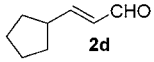
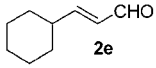
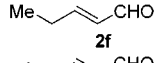
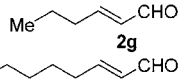
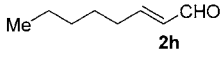
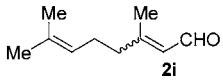
Table 3. Substrate Scope and Regioselectivity



entry	aldehyde **2**	*t* [h]	yield [%] [a]	**3**:**4** [b]	*ee* [%] [c]
1 [d,f]	 **2b**	47	65	78:22	93
2	 **2c**	96	71	74:26	93
3	 **2d**	60	48	78:22	92
4	 **2e**	96	60	65:35	93
5 [d,f]	 **2f**	26	55 [g]	16:84	92
6 [e]	 **2g**	48	48 [g]	17:83	76
7	 **2h**	48	45 [g]	28:72	70
8 [h]	 **2i**	72	72 [i]	<1:99	66 [j]

[a] Yield of isolated major product. [b] Determined by ^{1}H NMR. [c] *ee* of the major product determined by chiral HPLC. [d] Reaction was carried out at rt. [e] $CHCl_3$ was used as solvent. [f] AcOH (10 mol %) was used as acid additive. [g] *E*:*Z* = >99:1. [h] TFA (1 mol %) was used. [i] *E*:*Z* = 87:13, determined by ^{1}H NMR in the crude after reduction with $NaBH_4$ of **4i** to the corresponding alcohol. [j] Determined in the corresponding alcohol (*E*)-**5i**, see Supporting Information.

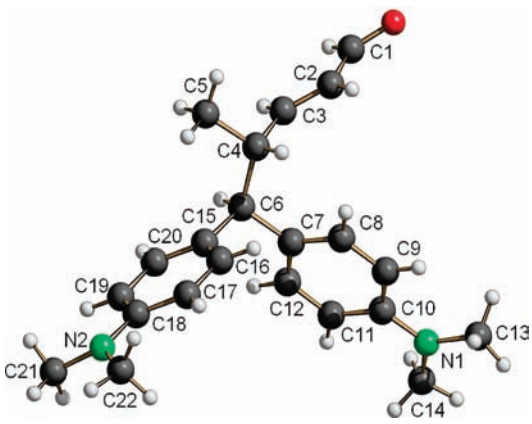
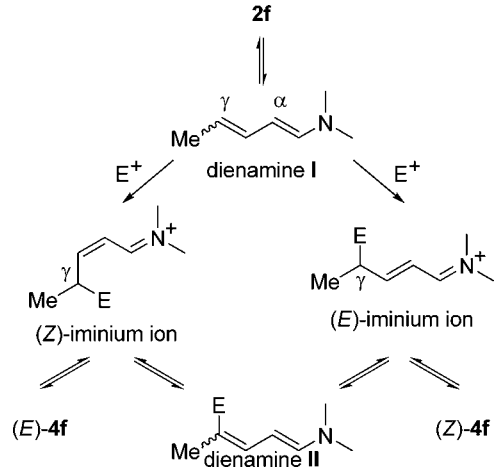


Figure 1. X-ray crystal structure of (*4R*)-**4f**.

dienamine **II** renders its protonation the stereodefining step, not the attack of dienamine **I** by the incoming bulky electrophile.

Scheme 3. Rationale for the Observed Products in the γ-Selective Alkylation of **2f**



In summary, we have developed a simple and highly enantioselective organocatalytic α- and γ-alkylation of α,β-unsaturated aldehydes catalyzed by commercially available diarylprolinol derivatives with stabilized carbocations as electrophiles.[24] To the best of our knowledge, this is the first enantioselective γ-alkylation of linear α,β-unsaturated aldehydes via dienamine activation. In addition, we have provided a basis for prediction of ambident reactivity for differently substituted α,β-unsaturated aldehydes using dienamine activation. The γ-substitution pathway is disfavored for γ-disubstituted aldehydes and shut down completely if one of the substituents is aromatic. Linear unbranched and β-substituted α,β-unsaturated aldehydes favor γ-substitution, and α-substituted aldehydes are unreactive using secondary amine catalysts.

Future research will be concerned with improvement of regiocontrol and the extension of dienamine catalysis toward other electrophiles.

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Supporting Information Available: Experimental procedures, NMR spectra, X-ray data, and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) After submission of our manuscript, two related reports were published. (a) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, DOI: 10.1002/anie.201004761. (b) Han, B.; Xiao, Y.-C.; Yao, Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, DOI: 10.1002/anie.201005296.