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Enantio- and Diastereoselective Synthesis of Substituted Tetrahydro-1*H*-isochromanes through a Dynamic Kinetic Resolution Proceeding under Dienamine Catalysis

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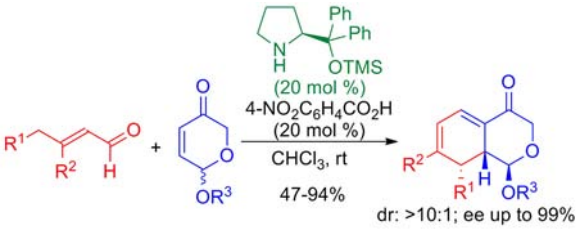
ABSTRACT



Racemic 5-acyloxydihydropyranones react with enolizable α,β-unsaturated aldehydes in the presence of a chiral secondary amine catalyst furnishing a wide range of differently substituted tetrahydro-1*H*-isochromanes with excellent results. The reaction relies on the activation of the enal by the catalyst through the formation of a dienamine intermediate, which undergoes a Diels–Alder/elimination cascade reaction. Moreover, the overall transformation also results in a highly efficient dynamic kinetic resolution process, furnishing the final adducts in high yields and excellent diastereo- and enantioselectivities.

The use of chiral secondary amines for catalyzing a variety of different chemical transformations in a stereocontrolled way has been the subject of intense research in the past decade.[1] In particular, the ability of these compounds to activate an aldehyde or a ketone toward its participation in a chemical reaction through the formation of an azomethine intermediate has shown to be a powerful approach for the α- or β-functionalization of aldehydes or enals *via* enamine[2]/iminium-cation radical[3] intermediates or *via* iminium ion intermediates[4] respectively. More recently, the application of the vinylogy concept has allowed expansion of the scope of this reactivity pattern to the γ-functionalization of α,β-unsaturated aldehydes or ketones through the formation of dienamine intermediates.[5] This approach has been exclusively developed in recent years, and consequently the number of examples reported in the literature regarding this topic is much more limited. Remarkably, this activation manifold has plenty of different possibilities to functionalize the starting material due to the rich reactivity profile presented in these dienamine intermediates, which are able to react through three different ways: (a) the classical *enamine reactivity*, where α-functionalization of the enal or enone occurs;[6] (b) the *vinylogous reactivity* which enables γ-functionalization;[7] and (c) *diene*

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(3) First example: Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

(4) Reviews: (a) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (b) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

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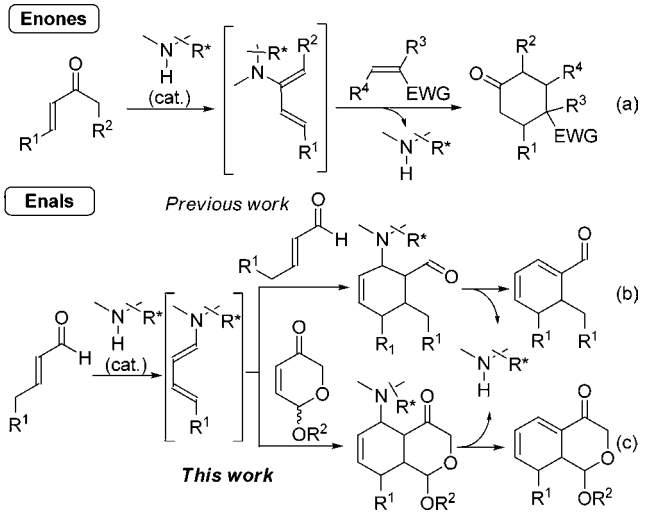
reactivity, in which the dienamine participates as an electron-rich diene in standard Diels–Alder-type reactivity.[8,9] In this latter case, although several examples exist using enones which react through a 2-amino-1,3-diene structure intermediate (eq a, Scheme 1),[8] the few precedents available in the literature with respect to the use of α,β-unsaturated aldehydes are related to their amine-catalyzed self-condensation,[9] which lead to the formation of cyclohexadienes (eq b, Scheme 1). This methodology is very limited in terms of reaction scope, and moreover the possible participation of an activated form of the Michael acceptor as the corresponding iminium ion (formed by condensation with the catalyst) cannot be ruled out. It is noteworthy to highlight that one of the main problems associated with this [4 + 2]-type reactivity of dienamine intermediates employing enals is the difficulty of releasing the catalyst, which has to proceed through an elimination process.

Scheme 1. Reactions of Enones and Enals Proceeding through Dienamine Activation *via* [4 + 2]-Type Reactivity



In this context, we have studied the behavior of racemic 2-substituted dihydropyranones such as those shown in eq c (Scheme 1) as suitable substrates in the reaction with enolizable enals under dienamine activation proceeding through a [4 + 2]-type reactivity. This transformation leads to the formation of enantiomerically enriched chroman analogues, which are pharmacologically relevant heterocycles present in a variety of natural products.[10] Moreover, this reaction also involves a dynamic kinetic resolution process in which the final adduct is obtained as a single diastereoisomer of high enantiomeric purity starting from racemic material. Another remarkable feature to be highlighted relies on the particular behavior of these dihydropyranones to form products from the [4 + 2] cycloaddition pathway, which is in deep contrast with other related highly electrophilic Michael acceptors such as nitroalkenes, which typically react with enolizable enals under dienamine activation furnishing either α- or γ-functionalization adducts.

We initially selected (*E*)-pent-2-enal (**1a**) and pyranone **2a** as model substrates. We started our study with the identification of the best chiral amine catalyst, using typical reaction conditions which involved working in $CHCl_3$ at rt and also incorporating benzoic acid as a cocatalyst which is known to facilitate the formation of this type of dienamine intermediates. As Table 1 shows, several diarylprolinol derivatives (**3a**–**e**) were found to be competent catalysts for the formation of adduct **4a**, achieving very high levels of enantio- and diasterocontrol, although in variable yields. From all the catalysts tested, the best results with respect to both yield and stereocontrol were obtained with catalyst **3b**, with the observation that simple diphenylprolinol **3a** performed very poorly in terms of conversion (compare entry 1 and 2) and that increasing the steric bulk too much at either the silyl substituent (catalyst **3c** in entry 3) or at the aryl groups (catalysts **3d** and **3e** in entries 4 and 5) led to lower yields of compound **4a**. On the other hand, imidazolidinone **3f** was inactive under the reaction conditions tried (entry 6). It should be pointed out that all catalysts afforded exclusively the corresponding cycloaddition adduct, without the presence of acyclic side products coming from α- or γ-additions being observed in any case.

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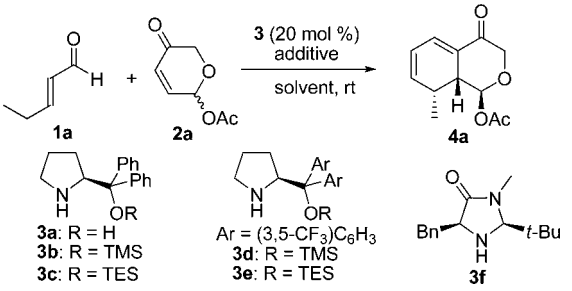
Table 1. Optimization of the Reaction Conditions[a]



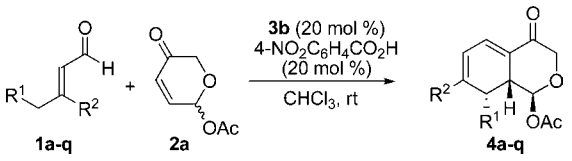
entry	cat.	additive	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a**	$PhCO_2H$	$CHCl_3$	37	6:1	93
2	**3b**	$PhCO_2H$	$CHCl_3$	60	>10:1	86
3	**3c**	$PhCO_2H$	$CHCl_3$	52	4:1	90
4	**3d**	$PhCO_2H$	$CHCl_3$	47	>10:1	86
5	**3e**	$PhCO_2H$	$CHCl_3$	37	>10:1	99
6	**3f**	TFA	$CHCl_3$	<5	n.d.[e]	n.d.[e]
7	**3b**	$PhCO_2H$	toluene	61	3:1	88
8	**3b**	$PhCO_2H$	THF	28	4:1	97
9	**3b**	$PhCO_2H$	EtOH	18	>10:1	93
10	**3b**	CH_3COOH	$CHCl_3$	73	6:1	92
11	**3b**	$4\text{-}NO_2C_6H_4CO_2H$	$CHCl_3$	67	>10:1	97
12	**3b**	*p*-TsOH	$CHCl_3$	19	6:1	98
13	**3b**	–	$CHCl_3$	76	3:1	88
14	**3b**	DABCO	$CHCl_3$	21	2:1	98

[a] Reactions were carried out on a 0.32 mmol scale employing 1.0 equiv of **1a** and 1.0 equiv of **2a** in the presence of 20 mol % of catalyst **3** and an additive in 5.0 mL of solvent (48 h). [b] Yield of pure major diastereoisomer after flash column chromatography purification. [c] Determined by NMR analysis of the crude product. [d] Determined by HPLC analysis (see Supporting Information). [e] n.d.: not determined.

Once the best catalyst was identified, we directed our efforts to improving the yield of the reaction. We initially tested the reaction using different solvents (entries 7–9) but without obtaining better results than those initially afforded in $CHCl_3$. Next, we evaluated the influence of Brønsted acid cocatalysts (entries 10–12) incorporating other different additives instead of the benzoic acid initially employed. In this sense, using a weaker carboxylic acid such as CH_3COOH ($pK_a = 4.76$)[11] resulted in an increase in the yield of the reaction but with a slight decrease in the diastereo- and enantioselectivity. In contrast, a slightly stronger carboxylic acid such as $4\text{-}NO_2C_6H_4CO_2H$ ($pK_a = 3.47$) furnished cycloadduct **4a** with a higher yield and stereoselectivity than those obtained initially. Using a stronger acid such as *p*-TsOH ($pK_a = -2.8$) resulted in very low conversions. We also evaluated the reaction in the absence of any cocatalyst, and although the yield of the reaction was higher than in all the preceding cases, the resulting diastereo- and enantioselectivity were significantly affected (entry 13). All these experiments indicate that there is a narrow pK_a window for which the Brønsted acid cocatalyst has a positive influence, which therefore implies that this parameter requires a careful optimization. Finally, we also evaluated the incorporation of a base cocatalyst (entry 14), but the transformation proceeded with very low conversion and poor diastereoselection. Taking into account all these results, we chose the conditions shown in entry 11 of Table 1 as the optimal ones for the projected transformation, proceeding next to carry out the reaction with a wide range of different α,β-unsaturated aldehydes in order to study the scope of the reaction.

(11) pK_a values measured in water.Perrin, D. D.; Serjeant, E. P.; Dempsey, B. *pKa Predictions for Organic Acids and Bases*; Champman and Hall: London, 1981.

Table 2. Scope of the Reaction[a]



entry	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	Me	H	**4a**	67	97
2	Et	H	**4b**	66	97
3	*n*-Pr	H	**4c**	64	96
4	*n*-Bu	H	**4d**	68	96
5	$n\text{-}C_5H_{11}$	H	**4e**	64	95
6	$n\text{-}C_6H_{13}$	H	**4f**	65	96
7	$n\text{-}C_7H_{15}$	H	**4g**	66	96
8	$PhCH_2$	H	**4h**	47	97
9	Ph	H	**4i**	81	92
10	$4\text{-}MeOC_6H_4$	H	**4j**	72	96
11	$4\text{-}MeC_6H_4$	H	**4k**	75	96
12	$4\text{-}FC_6H_4$	H	**4l**	63	91
13	$(Z)\text{-}CH_3CH_2CH{=}CHCH_2$	H	**4m**	55	98
14	2-thienyl	H	**4n**	72	76
15	$(CH_3)_2C{=}CHCH_2$	Me	**4o**	60	79
16	H	Me	**4p**	75	30
17	H	Ph	**4q**	91	35

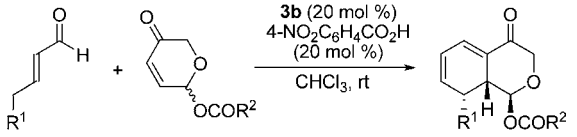
[a] All reactions were carried out using 0.32 mmol of **1a**–**q** and 0.32 mmol of **2a** in the presence of catalyst **3b** and $4\text{-}NO_2C_6H_4CO_2H$ in 5.0 mL of $CHCl_3$ at rt. [b] Yield of pure compound **4a**–**q** after flash column chromatography. [c] Determined by HPLC analysis (see Supporting Information).

As summarized in Table 2, all reactions studied proceeded in a completely regioselective manner and provided the desired adducts as single diastereoisomers. This methodology was successfully employed for β-alkyl monosubstituted α,β-unsaturated aldehydes **1a**–**h**, furnishing the corresponding final adducts with excellent enantioselectivities and good yields (entries 1–8). The use of γ-aryl substituted enals **1i**–**l** resulted in higher yields (entries 9–12) which can be explained in terms of their better ability to form a more stable conjugated dienamine intermediate. Aldehydes containing functionalized side chains like **1m**–**o** also reacted satisfactorily (entries 13–15). In addition, several β,β-disubstituted **1o**–**q** were also found to be good substrates in the reaction (entries 15–17), delivering the corresponding adducts **4o**–**q** in good yield

in all cases and also giving an excellent enantioselectivity for enal **4o** (entry 15), although a signifficant drop was observed in this parameter for those cases in which an unsubstituted dienamine intermediate was participating in the reaction as is in the case of aldehydes **4p** and **4q** (entries 16 and 17). Importantly, it should be noted that in most cases the reaction proceeded with yields over 50% and high enantio- and diastereoselectivies starting from a racemic material. This indicates that a dynamic kinetic resolution process is taking place, where one enantiomer of **2a** is reacting faster with the chiral dienamine intermediate, whereas the other enantiomer quickly racemizes in the reaction medium before participating in the transformation.

We also surveyed the use of other acyloxy substituents at the dihydropyranone reagent, and as can be seen in Table 3, the reaction proceeded with similar levels of eficiency than those obtained with the model substrate **2a** regardless of the nature of the substituent, obtaining good yields and stereoselectivities in all tested cases.

Table 3. Scope of the Reaction Using Different 3-Acyloxy-Substituted Pyranones[a]



1i, 1j, 1n 2b-e 4r-w

entry	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	Ph	*t*-BuO	**4r**	73	83
2	Ph	Ph	**4s**	85	85
3	Ph	4-ClC_6H_4	**4t**	88	87
4	Ph	4-$MeSC_6H_4$	**4u**	94	83
5	4-$MeOC_6H_4$	4-$MeSC_6H_4$	**4v**	66	99
6	2-thienyl	4-$MeSC_6H_4$	**4w**	68	97

[a] All reactions were carried out using 0.32 mmol of **1** and 0.32 mmol of **2** in the presence of catalyst **3b** and 4-$NO_2C_6H_4CO_2H$ in 5.0 mL of $CHCl_3$ at rt. [b] Yield of pure compound **4r**–**w** after flash column chromatography. [c] Determined by HPLC analysis (see Supporting Information).

The absolute configuration was unambiguously asigned as (1*S*,8*R*,8a*R*) by X-ray analysis of derivative **4w** (Figure 1). This configuration is in agreement with the stereochemical

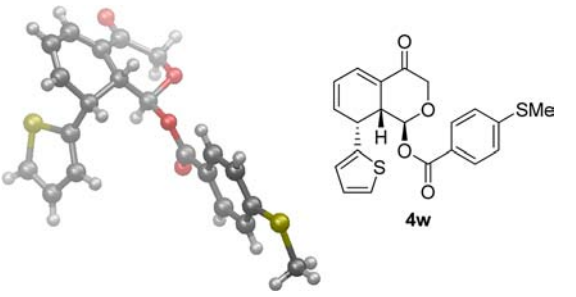


Figure 1. X-ray structure of compound **4w**.

outcome reported in the literature for other reactions in which catalyst **3b** has been involved for the activation of the substrate *via* dienamine catalysis and in which this type of intermediates subsequently engage in a Diels–Alder-type reaction.[5c]

In summary, we have developed an efficient procedure for the synthesis of isochromanes in good yields and excellent diastereo- and enantioselectivities, by exploiting the potential of dienamine catalysis to activate the γ-position of α,β-unsaturated aldehydes. In this sense, the reaction of a wide range of enals with racemic 4-acyloxy-substituted dihydropyranones in the presence of a chiral secondary amine catalyst leads to the formation of highly enantio- and diastereomerically enriched target compounds through a cascade [4 + 2]/elimination reaction in a dynamic kinetic resolution process.

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Supporting Information Available. Characterization of all new compounds, copies of their ^1H and ^{13}C NMR spectra and of the HPLC chromatograms used for the determination of enantiopurity. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.