Tandem Reactions

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Tertiary Amine Mediated Tandem Cross-Rauhut–Currier/Acetalization Reactions: Access to Functionalized Spiro-3,4-Dihydropyrans**

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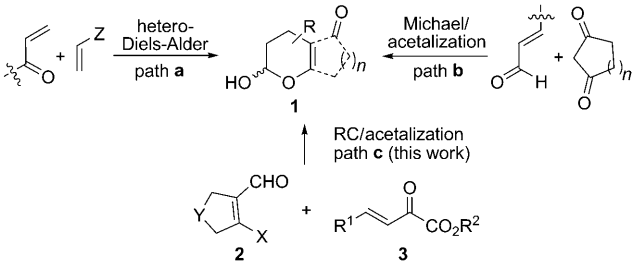
Continuing development in synthetic organic chemistry relies on discovering new, high yielding, and selective reactions. The Rauhut–Currier (RC) reaction (also known as the vinylogous Morita–Baylis–Hillman reaction), involving the coupling of one active alkene/latent enolate to a Michael acceptor, provides a unique method to create a new C–C bond between the α-position of one activated alkene and the β-position of a second alkene under the influence of a nucleophilic catalyst.[1] Whereas significant progress has recently been made with the intramolecular RC reaction as well as in the enatioselective variants,[2] the intermolecular RC reaction remains a challenge because of the lack of selectivity in cross-coupling reactions involving different activated alkenes.[3] In contrast, the products of an RC reaction, which are electron-deficient alkenes as well, are susceptible to polymerization. Notably, some RC reactions have been successfully incorporated into tandem or cascade processes to give access to structurally complex molecules.[4] Conceptually, these pioneering studies expanded the synthetic application of the RC reaction, even though substrates were limited to α,β-unsaturated ketones.

Substituted 3,4-dihydropyrans (**1**) are very useful precursors for the synthesis of carbohydrates and natural products.[5] A common way to access **1** is, for example, by an inverse-electron-demand hetero-Diels–Alder reaction between electron-rich alkenes with α,β-unsaturated carbonyl compounds (Scheme 1, path a).[6] Very recently, Rueping et al. and Jørgensen and co-workers independently reported an enatioselective domino Michael addition/cyclization of a 1,3-cycloalkanedione with an α,β-enal using a chiral secondary amine to afford bicyclic **1** (Scheme 1, path b).[7] Despite the myriad of approaches afforded by these reactions, few synthetic methods that produce quaternary carbon-containing spirocyclic structures by using nucleophilic promoters exist.[8] Herein we report an unprecedented tertiary amine mediated highly selective synthesis of spiro-3,4-dihydro-2*H*-pyrans from cyclic β-halo-α,β-unsaturated aldehydes (**2**) and β,γ-unsaturated



Scheme 1. Convergent access to substituted 3,4-dihydro-2*H*-pyrans (**1**).

α-keto ester (**3**) by a tandem cross-RC/acetalization reaction process (Scheme 1, path c).

Given their functionality, which offers a useful starting point for additional transformations, bromoenal **2a** and enone ester **3a** were reacted in presence of a Lewis base to explore the possibility of a cross-coupling.[9] We were pleased to discover that such a transformation could indeed be accomplished upon treatment with DBU in toluene, and more interestingly, a mixture of two anomers of hemiacetal **4a**, bearing a tethered vinyl bromide group and a spirocycle, was furnished in 36% yield (Table 1, entry 1).[10,11] The oxidation of this mixture with pyridinium chlorochromate (PCC) gave *trans*-lactone **5a** as a single diastereomer (Scheme 2). These results confirm: 1) the enolate can be generated from **2a** in situ to conduct a Michael addition; 2) γ-proton transfer leads to the formation of **4a**; and 3) the formation of the two carbon stereogenic centers is completely diastereoselective. Moreover, DBN also gave the product in a lower yield, whereas other nuclophilic tertiary amines such as DABCO, quinidine, DMAP, as well as the stronger base TMG, only afforded trace amounts of **4a** (Table 1, entries 2–6). In addition, $(n\mathrm{Bu})_3\mathrm{P}$ did not efficiently promote this reaction (Table 1, entry 7). Evidently, not only the basicity but also the nucleophility of DBU played a significant role in this tandem procedure.[12,13]

Encouraged by these results, we additionally optimized the reaction conditions using DBU as the Lewis base. Solvent screening (Table 1, entries 1 and 8–12) revealed that toluene was the most ideal as it led to the best result. A decrease in the reaction temperature to 0 °C improved the yield of product **4a** to 54% although an extended reaction time was required (Table 1, entry 13); whereas an additional lowering of the reaction temperature to −20 °C (Table 1, entry 14) caused a drop in the product yield to 45% after a reaction time of 16 hours. Upon changing the amount of DBU to 1.5 equiv-

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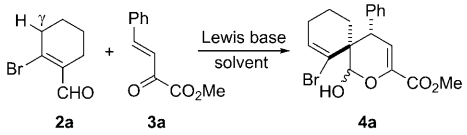
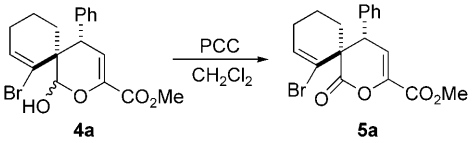
Table 1: Optimization of the coupling reaction of **2a** and **3a**.[a]



2a **3a** **4a**

Entry	Lewis base (equiv)	Solvent	T [°C]	t [h]	Yield [%][b]
1	DBU (1.0)	toluene	RT	1	36
2	DBN (1.0)	toluene	RT	1	27
3	DABCO (1.0)	toluene	RT	12	trace
4	quinidine (1.0)	toluene	RT	12	trace
5	DMAP(1.0)	toluene	RT	12	trace
6	TMG (1.0)	toluene	RT	2	trace
7	$(n\mathrm{Bu})_3\mathrm{P}$ (1.0)	toluene	RT	12	trace
8	DBU (1.0)	DMF	RT	1	trace
9	DBU (1.0)	CH_3CN	RT	1	trace
10	DBU (1.0)	CH_2Cl_2	RT	1	21
11	DBU (1.0)	THF	RT	1	18
12	DBU (1.0)	*t*BuOH	RT	1	11
13	DBU (1.0)	toluene	0	8	54
14	DBU (1.0)	toluene	−20	16	45
15	DBU (0.5)	toluene	0	12	43
16	DBU (1.5)	toluene	0	3	64
17	DBU (3.0)	toluene	−20	3.5	52

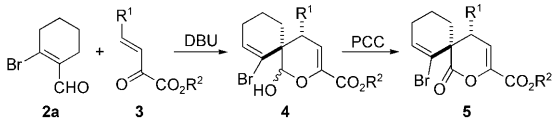
[a] Reaction conditions: **2a** (0.75 mmol, 1.5 equiv), **3a** (0.5 mmol, 1.0 equiv), and Lewis base in solvent (5.0 mL). [b] Yield of isolated product. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DBN = 1,5-diazabicyclo[4.3.0]non-5-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMAP = 4-dimethylaminopyridine, TMG = 1,1,3,3-tetramethylguanidine.



4a **5a**

Scheme 2. Conversion of **4a** into **5a**.

Table 2: Tandem coupling reaction of **2a** with enones **3** and the oxidation of product **4** into lactones **5**.[a]



2a **3** **4** **5**

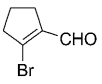
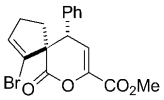
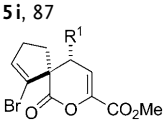
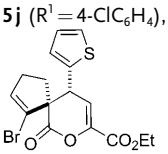
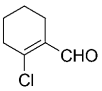
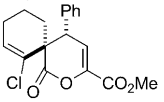
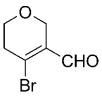
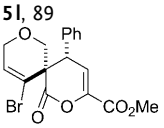
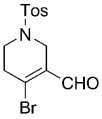
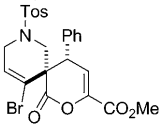
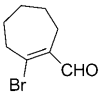
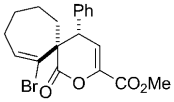
Entry	3	R^1	R^2	t [h][b]	4,Yield [%][c]	5,Yield [%][d]
1	**3a**	Ph	Me	3	**4a**, 64	**5a**, 91
2	**3b**	Ph	Et	2.5	**4b**, 66	**5b**, 95
3	**3c**	4-FC_6H_4	Me	1.5	**4c**, 55	**5c**, 91
4	**3d**	4-$CH_3C_6H_4$	Me	3	**4d**, 63	**5d**, 96
5	**3e**	3-$NO_2C_6H_4$	Et	1	**4e**, 55	**5e**, 92
6	**3f**	4-$CH_3OC_6H_4$	Et	6	**4f**, 51	**5f**, 85
7	**3g**	*N*-tosyl-indol-3-yl	Et	5	**4g**, 48[e]	**5g**, 81
8	**3h**	2-furyl	Et	4.5	**4h**, 45	**5h**, 65

[a] Reaction conditions: 1. **2a** (0.75 mmol), **3** (0.5 mmol.), DBU (0.75 mmol), 0 °C, toluene (5.0 mL); 2. PCC (1.5 equiv), reflux, CH_2Cl_2. [b] Time for consuming **3**. [c] Yield of the mixture of two anomers after flash chromatography. [d] Yield of isolated product. [e] Reaction was run in CH_2Cl_2. tosyl = 4-toluenemethanesulfonyl.

alents at 0 °C, the optimal balance of the reaction rate and yield was obtained (Table 1, entry 16). When 0.5 equivalents or 3.0 equivalents of DBU was used instead, the yield of **4a** fell to 43 % (0 °C, 12 h) and 52 % (−20 °C, 3.5 h), respectively (Table 1, entries 15 and 17).

Next, the cross-RC/acetalization of **2a** with a variety of enones **3** under the optimized reactions conditions were investigated. As shown in Table 2, the electron-rich or electron-poor aryl-substituted substrates **3a–f** clearly underwent cross-cyclization in moderate to good yields. Electron-poor substrates underwent conversion more quickly than their electron-rich counterparts, albeit with a slightly lower yield[14] (Table 2, entries 3, 5, versus 6). Moreover, the size of ester substitutent (R^2) of **3** had little effect on the tandem process, as **3b** (R^2 = ethyl) gave **4b** in almost similar yield to that of **4a** from **3a** (R^2 = methyl; Table 2, entries 1 and 2).

Table 3: Substrate scope of the tandem coupling of enals **2** and enones **3**.[a]

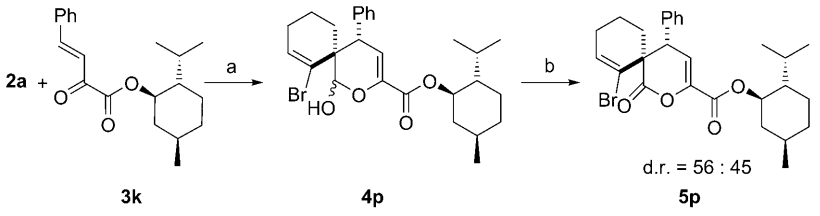
Entry	2	3	t [h][d]	4, Yield [%][e]	5, Yield [%][f]
					
1	**2b**	**3a**	3	**4i**, 65	**5i**, 87 
2	**2b**	**3i**[b]	4	**4j**, 62	**5j** (R^1 = 4-ClC_6H_4), 92 
3	**2b** 	**3j**[c]	5	**4k**, 51	**5k**, 83 
4	**2c** 	**3a**	4.5	**4l**, 59	**5l**, 89 
5	**2d** 	**3a**	2.5	**4m**, 91	**5m**, 85 
6	**2e** 	**3a**	3	**4n**, 42	**5n**, 72 
7	**2f**	**3a**	24	**4o**, n.r.	**5o**, n.r.

[a] Reaction conditions: a) **2** (0.75 mmol), **3** (0.5 mmol.), DBU (0.75 mmol), 0 °C, toluene (5.0 mL); b) PCC (1.5 equiv), CH_2Cl_2, reflux. [b] **3i**: R^1 = 4-ClC_6H_4, R^2 = Me. [c] **3j**: R^1 = 2-thienyl, R^2 = Et. See reaction equation in Table 2 for structure, Tos = 4-toluenesulfonyl. [d] Time for consuming **3**. [e] Yield of the mixture of two anomers after flash chromatography. [f] Yield of isolated product. n.r. = no reaction.

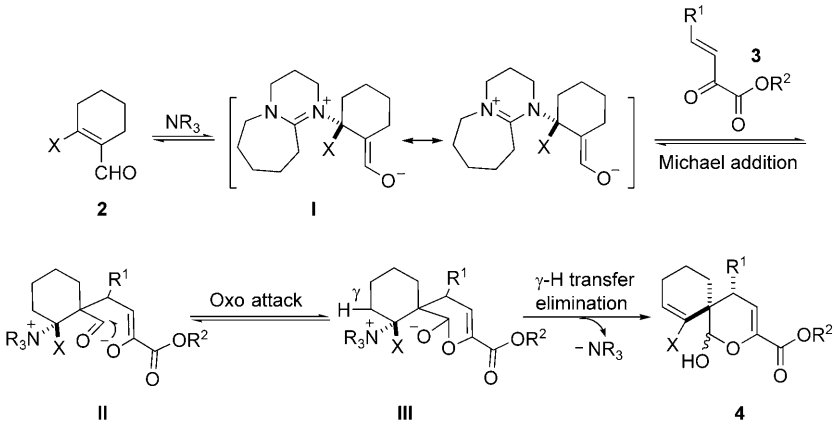
Heteroaromatic compounds **3**, including a furan and an indole, were also successfully employed in this reaction. Nevertheless, the product **4g** was obtained in 48% yield when using CH_2Cl_2 as the solvent; **3g** displayed poor solubility in toluene.

Whereas the tandem reaction of the five-membered and heteroatom-substituted six-membered enals **2b–e** proceeded smoothly to produce the expected hemiacetals of **4**, the seven-membered enal **2f** did not undergo reaction under the reaction conditions (Table 3). Notably, the oxygen-containing enal **2d** completed the reaction within 2.5 hours and furnished **4m** in excellent yield, and *N*-tosyl-protected enal **2e** only gave **4n** in 42% (Table 3, entries 5 and 6). These results can be rationalized by steric and electronic effect considerations: an electron-withdrawing oxygen atom could enhance the acidity of the γ proton and thereby promote the reaction of **2d**; in contrast, a bulky tosyl group may lead to an unfavorable conformation for the corresponding transformation of **2e**.

Preliminary studies on an asymmetric variant of this tandem reaction was tested with (−)-menthyl ester **3k** and enal **2a** as the substrates under the previous optimized reaction conditions (Scheme 3). Although **3k** underwent coupling to give **4p** in 74% yield after 2.5 hours, **5p** (product isolated after oxidation with PCC) was obtained with poor diastereoselectivity (d.r. 56:45) as determined by ^{1}H NMR analysis.



Scheme 3. Asymmetric tandem coupling of **2a** with **3k**. Reaction conditions: a) DBU, toluene, 2.5 h, 74%; b) PCC, CH_2Cl_2, 7.5 h, 78%.



Scheme 4. Possible mechanism for the tertiary amine mediated cross-Rauhut–Currier/acetalization of **2** and **3**. NR_3 = DBU, R^1 = aryl, R^2 = alkyl, X = Br, Cl.

Although detailed mechanistic studies have not been undertaken, a plausible mechanism for the tertiary amine mediated tandem cross-Rauhut–Currier/acetalization reaction is illustrated in Scheme 4. Conjugate addition of DBU to enal **2** provides enolate **I**, which could be stabilized by resonance as proposed for MBH reactions.[15] Subsequent intermolecular Michael addition onto enone **3** affords zwitterionic intermediate **II**.[16] This newly formed enolate undergoes intramolecular acetalization with the tethered aldehyde rendering spirocyclic alkoxide **III** instead of protonation as in classic RC reaction. Finally, γ-proton transfer ensues, directly or assisted by DBU, yielding hemiacetal **4** with regeneration of the amine catalyst.

In summary, we have presented an efficient, tertiary amine mediated cross-Rauhut–Currier/acetalization of cyclic β-haloenals and β,γ-unsaturated α-ketoesters. The tertiary amine serves not only as a nucleophilic promoter to conduct a cross-RC reaction but probably also as a mediator of γ-proton transfer. Significantly, functionalized spiro-3,4-dihydro-2*H*-pyran derivatives with an α quaternary carbon center and an adjacent vinyl bromide group in skeleton are easily assembled from simple substrates by this method. Experiments designed to explore the scopes, limitations, and asymmetric variants of this reaction are ongoing and will be reported in due course.

Experimental Section

Representative procedure (Table 2, entry 1): DBU (114 mg, 0.75 mmol) was added to a solution of cyclic β-bromo-enal **2a** (142 mg, 0.75 mmol) and β,γ-unsaturated α-keto ester **3a** (95 mg, 0.5 mmol) in 5 mL of anhydrous toluene at 0 °C under N_2 atmosphere. The reaction mixture was stirred at this temperature for 3 h until complete consumption of **3a** (as observed by TLC methods). The reaction was quenched with 5 mL of saturated aqueous $NaHCO_3$ and extracted with EtOAc (10 mL ×3). After washing with 10 mL of brine, the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc 5:1) to afford compound **4a**: 121 mg, 64%; colorless oil; ratio of the two anomers of **4a** = 93:7 (from ^{1}H NMR analysis); ^{1}H NMR (400 MHz, $CDCl_3$, TMS, major anomer) δ = 7.31–7.25 (m, 5H), 6.42 (dd, J = 2.8 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 5.48 (d, J = 3.2 Hz, 1H), 4.38–4.36 (m, 2H), 3.86 (s, 3H), 1.98–1.90 (m, 1H), 1.88–1.82 (m, 1H), 1.63–1.60 (m, 2H), 0.02–(−0.09) ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS, major anomer) δ = 162.5, 142.1, 138.7, 136.7, 128.8, 128.1, 127.3, 126.0, 114.6, 99.1, 52.5, 45.6, 45.2, 27.2, 2.5, 17.8 ppm; IR (film): $\tilde{\nu}$ = 3481, 2951, 2871, 1731, 1652, 1440, 1287, 1277 cm^{-1}; HRMS (ESI): calculated for $C_{18}H_{19}BrO_4Na$ $[M+Na]^+$ 401.0359, found 401.0353.

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Keywords: cross-coupling · cyclization · Lewis bases · Michael addition · tandem reactions

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