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Enantioselective Synthesis of Chromanones via a Peptidic Phosphane Catalyzed Rauhut–Currier Reaction

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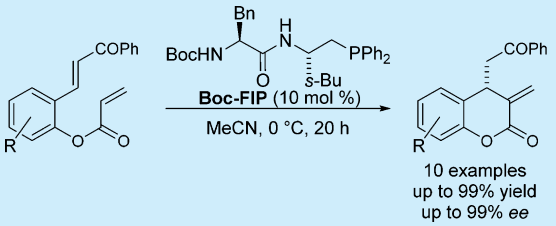
Supporting Information

ABSTRACT: The enantioselective intramolecular Rauhut–Currier reaction has been developed using a bifunctional dipeptidic phosphane catalyst, providing a direct access to biologically active α-methylene-δ-valerolactones in high yields and enantiomeric excesses. The novel catalyst is accessible in only four steps from commercial sources and exhibits unusual binding selectivities for a small molecule, suggesting the possibility for long-range interactions between the catalyst and the substrate.



Over the past two decades the field of phosphane organocatalysis expanded greatly providing a broad range of new transformations.[1] Based on the nucleophilicity of the phosphane, the most common mode of action of phosphanes is the Michael addition to an activated double bond revealing the latent enolate. The nature of the enolate and its next coupling partner subsequently dictates mechanistically distinct reaction pathways resulting in diverse transformations such as Morita–Baylis–Hillman (MBH),[2] Rauhut–Currier (RC),[3] and multiple annulation reactions.[4]

Known as one of the oldest phosphane-catalyzed reactions, RC was first reported as early as 1963 and is a highly atom economic dimerization of two Michael acceptors.[5] However, in contrast to the related MBH and annulation reactions, RC often lacks selectivity, and hence, new enantioselective RC reactions were reported only rarely.[6] The first successful enantioselective RC reaction was published by Miller utilizing a cysteine based catalyst in 2007.[6a,e−g] In the following years different groups contributed to the catalyst development utilizing rhenium metallocene complexes,[6b] scandium salts,[6c] prolinol,[6d] thiourea,[6h] and quinine based compounds.[6i] Unfortunately, the substrate scope was usually limited to specific Michael acceptors and the enantioselectivities did not always reach synthetically useful values. More recently, a significant improvement was achieved by the introduction of amino acid derived phosphanes by Wu[6j] and Sasai.[6k,l] Complementing the Lewis basicity of the phosphane with a Lewis acidic functionality, the new generation of bifunctional catalysts accessed several RC products in extraordinary yields and selectivities. However, even those catalysts have their limits, and hence, the development of new catalysts for an independent RC reaction is still ongoing research.[6m,7]

We became interested in this research by envisaging the synthesis of chromanone **1** via the RC cyclization of chalcone derivative **2** (Figure 1). Such α-methylenelactones are a common structural motif in many thousands of natural products, exhibiting a broad range of diverse biological activities.[8] In particular, synthetic and natural α-methylene-δ-valerolactones were shown to have antitumor (**3**,[9] **7**[10]), antibacterial (teucriumlactone **4**,[11] crassin **5**[12]), and antimalarial (artemisitene **6**[13]) activities among others.

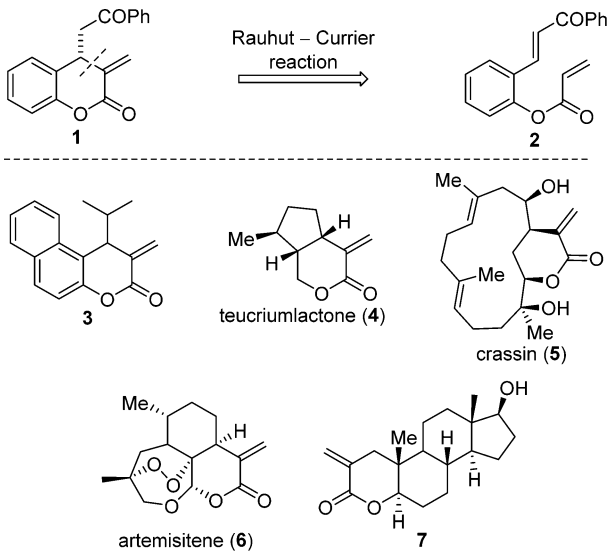


Figure 1. Retrosynthetic analysis of chromanones (top); biologically active α-methylene-δ-valerolactones (bottom).

We started our investigation exploring the racemic RC reaction of chalcone **2** using homoleptic phosphanes such as triphenylphosphane or trialkylphosphanes (Table 1, entry 1). Surprisingly, in contrast to the previous reports on the synthesis of α-methylenelactones via the RC reaction, only very low conversions were observed after 20 h.[6k,l] As opposed to this, heteroleptic phosphanes such as diphenyl-methylphosphane or dicyclohexyl-phenylphosphane performed this reaction well leading to the desired product **1** in 70–74% yield (entry 2).

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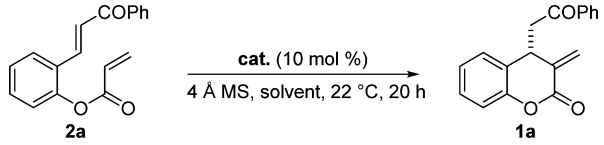
Table 1. Optimization of Reaction Conditions[a]



entry	cat.	solvent	yield [%][b]	ee [%][c]
1	Ph_3P, c-Hex_3P, n-Bu_3P	$CHCl_3$	<10	–
2	$MePPh_2$, c-Hex_2PPh	$CHCl_3$	70–74	–
3	**11d**	$CHCl_3$	67	<5
4	**11d**	CH_2Cl_2	71	43
5	**11d**	hexane	29	51
6	**11d**	toluene	15	−26[d]
7	**11d**	EtOAc	30	43
8	**11d**	Et_2O	22	<5
9	**11d**	THF	14	33
10	**11d**	acetone	36	64
11	**11d**	DMSO	33	29
12	**11d**	i-PrOH	64	10
13	**11d**	MeCN	64	72
14[e]	**11d**	MeCN	96	84
15[e]	**8**	MeCN	37	70
16[e]	**9**	MeCN	75	60
17[e]	**10**	MeCN	42	−14[d]
18[e]	**11a**	MeCN	88	76
19[e]	**11b**	MeCN	32	<5
20[e]	**11c**	MeCN	65	70
21[e]	**11e**	MeCN	90	82
22[e]	**11f**	MeCN	61	76
23[e]	**11g**	MeCN	25	32
24[e]	**12**	MeCN	74	68
25[e]	**13**	MeCN	93[f]	97[f]

[a]Conditions: **2a** (0.07 mmol) in 0.7 mL of solvent. [b]Yields were determined via ^{1}H NMR experiment using acetophenone as an internal standard. [c]Ee's were determined via HPLC analysis on a chiral stationary phase. [d]Opposite enantiomer was formed predominantly. [e]At 0 °C. [f]Yield and ee determined on isolated product after column chromatography.

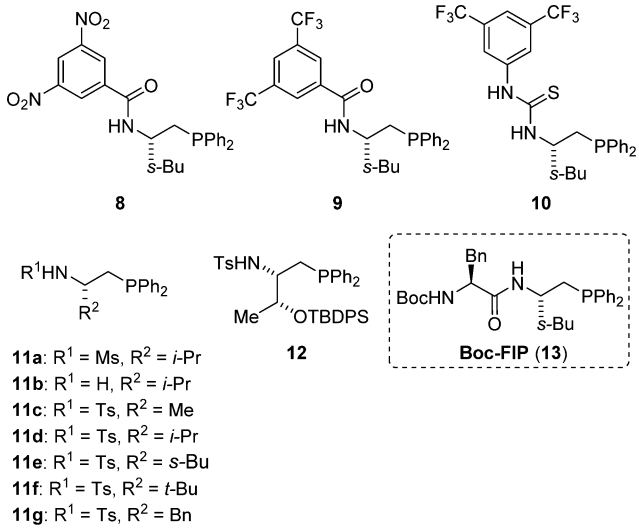


Figure 2. Catalysts used for optimization of the Rauhut–Currier reaction. TBDPS = *tert*-butyldiphenylsilyl. Boc = *tert*-butyloxycarbonyl.

We kept this in mind when we started the development of the enantioselective version of this reaction utilizing the heteroleptic valine derived catalyst **11d** at room temperature (22 °C) in chloroform. Indeed the desired product **1** was observed in moderate yields but, again contrary to the previous reports,[6k,l] without any stereoinduction (entry 3). Fortunately, rescreening the solvents (entries 3–13) identified the polar aprotic solvent acetonitrile as being best able to assist the catalyst **11d** to control the stereogenic center, yielding the δ-valerolactone **1** in 64% yield and 72% *ee* (entry 13). In addition, lowering the temperature to 0 °C further improved the *ee* up to 84% as well as the yield to 96% due to reduced formation of coumarin side product (entry 14). In order to further improve the enantioselectivity of the RC reaction we synthesized different amino acid derived catalysts **8**–**13** aiming for variation of the side chain as well as the hydrogen bonding properties by changing the *N*-attached substituent (Figure 2). However, we could not find any direct correlation between the increased *NH*-acidity of the Lewis acid group and the enantioselectivity (Table 1, entries 15–19). For instance, in comparison to the tosyl group in the catalyst **11d**, a less acidic acyl group (**8**, **9**) as well as a significantly more acidic thiourea group (**10**) led all to lower *ee*-values (entries 15–17). Nevertheless, the presence of the Lewis acidic group in the catalyst was proven to be essential for enantioselectivity as was shown by testing the *N*-unsubstituted aminocatalyst **11b** (entry 19). Subsequently, catalysts **11c–g** bearing different side chains were applied in the outlined RC reaction (entries 20–24) as we hoped to observe a direct coherence between the steric bulk of the side chain and the enantioselectivity. Indeed all the catalysts led to the desired product **1**, but the optimum for enantioselectivity was not around highly sterically hindered *tert*-leucine or threonine based catalysts **11f** and **12** (entries 22, 24) but around valine or isoleucine derived catalysts **11d** and **11e** respectively (entries 14, 21), which also showed higher yields.

Recently, some dipeptidic phosphane catalysts were introduced by the Lu group for several mechanistically related annulation reactions.[4b,f,g] The extremely high yields and enantioselectivities which were achieved by the Lu group were highly encouraging; however the syntheses of their catalysts require more than 10 steps. This motivated us to develop dipeptidic phosphane catalysts accessible in fewer steps for our reaction, so we decided to attach a second amino acid to the most efficient single amino acid derived catalyst **11d**. For this, we chose Boc-protected phenylalanine as a commercially available and relatively inexpensive coupling partner. Fortunately, the resulting Boc-protected phenylalanine-isoleucine derived phosphane **Boc-FIP** (**13**) has performed the desired RC reaction in excellent yields and enantioselectivities (entry 25).

With the optimized reaction conditions in hand we continued our investigation of the reaction with the substrate scope (Scheme 1). Eleven differently substituted substrates were synthesized and subjected to the reaction conditions. With the exception of the nitro-compound **1f**,[15] the obtained yields for all tested compounds were good to excellent (50–99%) while electron-rich substrates performed better than the electron-poor ones due to the increased formation of coumarin side products in the latter case. As for the enantioselectivities, most chalcones **2** gave high ee's (up to 99%). However, surprisingly, 5-substituted chromanones **1e** and **1k** were obtained only in moderate enantioselectivities (50% and 43% ee, respectively). Interestingly, as we repeated the entire substrate scope with the catalyst **11d** this unusual substrate

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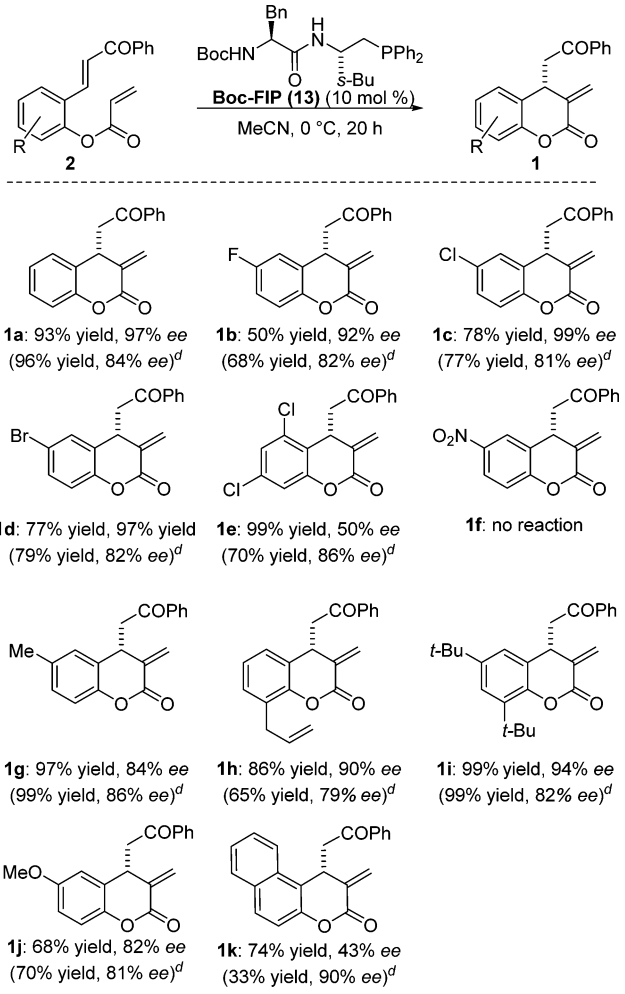
Scheme 1. Scope of the Rauhut–Currier Reaction[a,b,c]

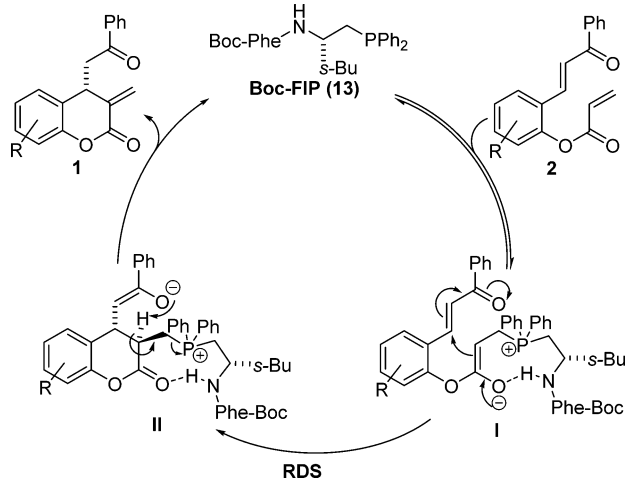


[a]Conditions: **2** (0.5 mmol) in 5 mL of solvent. [b]Yields and ee's were measured on isolated products. [c]Ee's were determined via HPLC analysis on a chiral stationary phase. The absolute configuration was unambiguously determined via X-ray crystallographic analysis on compound **1d**.[14] All the other stereogenic centers were assigned in analogy. [d]In brackets: yields and ee's obtained using catalyst **11d**.

binding selectivity was not presented and all chalcones **2** were cyclized with similar enantioselectivities around 80%–90% *ee* (Scheme 1, values in brackets). This effect cannot be explained by the usual steric or electronic effects and hydrogen bonding, which may indicate some long-range interaction between the second amino acid and the aromatic ring of the substrate.

The proposed mechanism is summarized in Scheme 2. The reaction starts with the nucleophilic attack of the phosphane catalyst **13** onto the most reactive terminal double bond. As was discussed above, it is likely that the resulting intermediate **I** contains hydrogen bonding between the most basic enolate oxygen and the acyl-nitrogen. Furthermore, due to the conformational restriction caused by this hydrogen bond the phenyl groups on the phosphorus atom will avoid 1,3-steric clash and point away from the bulky *sec*-butyl group. In the resultant conformation, the PPh_2-group blocks the *Re*-face of the enolate and the intramolecular Michael addition occurs from the opposite site explaining correctly the stereochemical outcome. The mechanistic cycle is completed by the *β*-

Scheme 2. Proposed Mechanism



elimination in the intermediate **II** liberating the product **1** and the catalyst **13**.

In order to obtain more insight into the mechanism, we have additionally determined three fundamental kinetic parameters (the enthalpy of activation $\Delta_r H^{\ddagger}$, the entropy of activation $\Delta_r S^{\ddagger}$, and Hammett's reaction constant ρ) for the reaction of chalcone **2a** toward chromanone **1a** using catalyst **11d** in deuterated acetonitrile. The enthalpy of activation $\Delta_r H^{\ddagger} = 12.8 \pm 2.1$ kJ·mol^{-1} indicates that in the transition state more bonds are broken rather than formed. The entropy of activation $\Delta_r S^{\ddagger} = -275.1 \pm 6.7$ J·K^{-1}·mol^{-1} suggested a decrease of freedom in the transition state. Finally, Hammett's reaction constant $\rho = 2.0 \pm 0.2$ showed that the reaction proceeds faster with electron-deficient substituents. Hence, overall all three parameters support the assumption that the intramolecular Michael addition is the rate-determining step.

In summary, we have developed an enantioselective Rauhut–Currier reaction of chalcones **2** to chromanones **1** utilizing a novel polyfunctional dipeptidic phosphane catalyst **13**. This catalyst is accessible in only four steps from cheap commercially available amino acids making it more practical than previous reports on dipeptidic phosphane catalysts.[16] Overall the new catalyst performed with good to excellent yield and enantioselectivities, furthermore, exhibiting an unusual substrate binding selectivity for a small molecule catalyst.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, and HPLC chromatograms. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00971.

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Notes

The authors declare no competing financial interest.

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(14) CCDC-1055502 contains the supplementary crystallographic data for the compound **1d** reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) ^{1}H NMR experiments indicated that the catalyst may attack the disubstituted double bond in this case. This would trap the catalyst since the formation of a seven membered ring is kinetically unfavorable and, hence, prevent further reaction.

(16) For details on catalyst synthesis please see p S4 in the Supporting Information.

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