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Enantioselective Intramolecular Crossed Rauhut–Currier Reactions through Cooperative Nucleophilic Activation and Hydrogen-Bonding Catalysis: Scope and Mechanistic Insight

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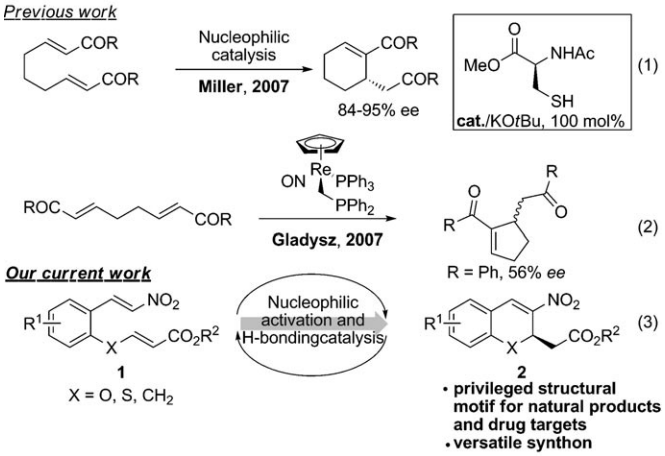
Abstract: A highly efficient and enantioselective intramolecular crossed Rauhut–Currier (RC) reaction of nitroolefins with tethered enonates has been developed through cooperative nucleophilic activation and a hydrogen-bonding catalytic strategy (≤98% *ee* and 98% yield). The reaction features simple experimental procedures and is completely chemoselective and atom-economic in character. The potential synthetic applications have been demonstrated by the conversion of the RC reaction products into biologically and pharmaceutically valuable compounds with highly diastereoselectivity. In addition, computational investigations were employed to support the proposed mechanism and to obtain a good understanding of the origin of the stereoselectivity in RC reactions.

Keywords: asymmetric catalysis · cascade reactions · hydrogen bonds · Michael addition · Rauhut–Currier reaction

Introduction

Since 1963, Rauhut–Currier (RC) and Morita-Baylis-Hillman (MBH) reactions have emerged as unique and valuable carbon-carbon bond-forming protocols.[1] Whereas remarkable progress has been achieved in regard to the MBH reaction, the RC transformation remains largely undeveloped. The key challenge has been the difficulty in controlling the selectivity of the cross-coupling reactions, which involve two different activated alkenes.[2] In addition, some activated alkenes only react sluggishly or provide undesired byproducts under normal conditions. In 2002, Krische and Roush independently disclosed a R_3P-catalyzed intramolecular version of the RC reaction that employed bis-enone substrates.[3b,c] These pioneering studies cleverly addressed the issue of selectivity in RC reactions. As a consequence, extensive efforts have been devoted toward increasing the power of the RC process over the past several years.[4] Surprisingly, almost all of these catalytic protocols primarily utilized phosphine-based catalysts and were typically limited to the use of bis-enones or enone-tethered α,β-unsaturated esters. In particular, the enantioselective variants of the RC reactions are extremely rare due to the lack of efficient catalytic systems.[5] In 2007, Aroyan and Miller demonstrated that a protected cysteine moeity acted as an efficient nucleophilic promoter to mediate an enantioselective intramolecular RC reaction [Eq. (1)].[5b] Shortly after, Seidel and Gladysz developed a chiral rhenium/phosphine complex catalyst for the intramolecular RC reaction of bis-enones, thus giving a cycloisomerization product with moderate enantiomeric excess [Eq. (2)].[5c] Wang and co-workers reported in 2008 a one-pot enantioselective Michael/Michael cascade reaction to provide highly functionalized thiochromenes in excellent yields and stereoselectivities.



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As described by the authors, the reaction may involve a dynamic kinetic resolution-mediated RC reaction procedure.[6] Recently, Christmann et al. generated chiral cycloalkenes through a dienamine-activated crossed intramolecular RC-type reaction in an excellent study.[7] Despite the superior Michael acceptor ability of the nitroalkene and the well-documented synthetic utility of the nitro group, the intramolecular RC-type reaction of conjugated nitroalkenes has not received much attention to date.[8] Thus, further extension of the scope of such viable substrates and the development of asymmetric versions of RC reactions with synthetically useful enantioselectivities are still highly desirable.

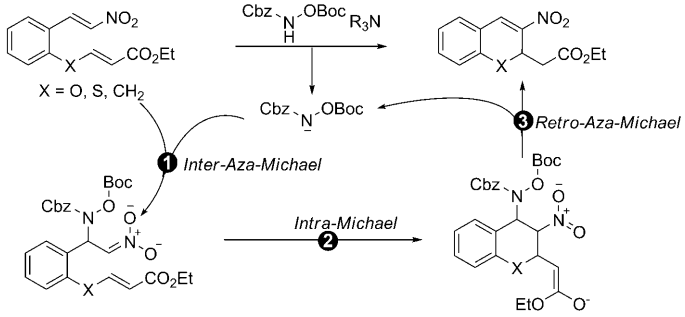
The continuous exploration of novel and more efficient methods for the synthesis of heavily functionalized and biologically valuable chiral scaffolds has been of long-standing interest to the chemical community.[9] In this context, the chiral chromene plays an important role in various medicinal compounds that have a broad and interesting range of biological activities[10] and becomes a valuable architectural platform for developing new synthetic methodologies. Therefore, a number of spectacular advances have been made for the construction of this "privileged" structural motif, such as the Pt-catalyzed cyclization of chiral precursors,[11] ring-closing metathesis,[12] and organocatalytic domino oxo-Michael-aldol-dehydration reactions.[13] Despite this great progress, the search for more efficient and highly enantioselective approaches to construct the chromene skeleton is still extremely attractive.

Recently, the concept of combining two distinct catalytic entities, which work in concert, has been considered to be state of the art in asymmetric synthesis.[14] The synergistic activation by such a two-component catalyst system usually enables efficient stereocontrol in a wide range of reactions that were previously unsuccessful.[15] In 2008, we disclosed an unprecedented reaction of sulfur ylides with nitroolefins sequentially catalyzed by thiourea and 4-dimethylaminopyridine (DMAP) to afford diverse and structurally complex oxazolidin-2-ones.[16] Encouraged by the potential of this cooperative catalysis, we became interested in the possibility of using a similar strategy to carry out an enantioselective RC reaction. Herein, we report the successful execution of this idea and describe highly enantioselective RC reactions of nitroolefins with tethered α,β-unsaturated esters [Eq. (3)].

This methodology provides an efficient access to highly functionalized 2*H*-chromenes, 2*H*-thiochromenes, and 1,2-dihydronaphthalenes, all in an atom-economical and chemoselective fashion (Scheme 1).[17] Furthermore, to understand this new RC reaction, a series of experimental and computational studies on the mechanism and the determining step of the stereoselectivity will be presented.

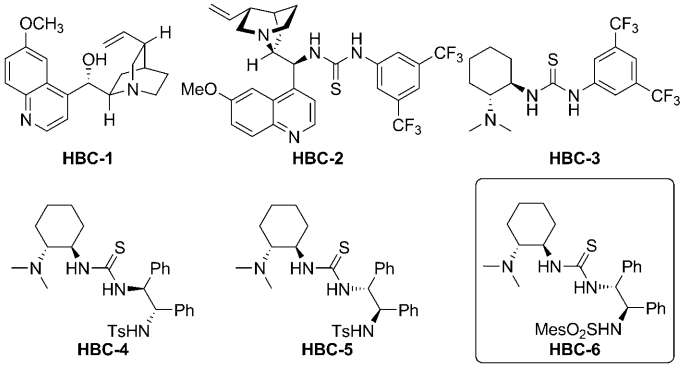
Results and Discussion

Evaluation of intramolecular crossed Rauhut–Currier reaction conditions: Our investigation began with the intramolecular reaction of nitroolefin enoate **1a**.[18] In search of an efficient catalytic system, we decided to use benzyl *tert*-butoxycarbonyloxycarbamate (**3**)[19] as the nucleophilic promoter because of the intrinsic ability of this compound to initiate a reversible Michael addition reaction. Table 1 summarizes our efforts to identify a viable hydrogen-bonding catalyst (HBC) for the process.[20] The combination of achiral **3**



Scheme 1. Proposed pathway for the Rauhut–Currier cyclization reaction. Boc = *tert*-butoxycarbonyl, Cbz = carbobenzyloxy.

Table 1. Evaluation of intramolecular crossed Rauhut–Currier reaction conditions.[a]



Entry	Catalyst	Solvent	*T* [h]	Yield [%][b]	*ee* [%][c]
1	**HBC-1**	CH_2Cl_2	24	74	−50
2	**HBC-2**	CH_2Cl_2	24	89	−72
3	**HBC-3**	CH_2Cl_2	24	67	70
4	**HBC-4**	CH_2Cl_2	24	60	62
5	**HBC-5**	CH_2Cl_2	24	92	82
6	**HBC-6**	CH_2Cl_2	24	98	80
7[d]	**HBC-6**	CH_2Cl_2	40	85	86
8[d]	**HBC-6**	$CHCl_3$	16	94	86
9[d]	**HBC-6**	Et_2O	120	83	80
10[d]	**HBC-6**	CH_3CN	30	83	80
11[d]	**HBC-6**	CH_3OH	72	94	64
12[e]	**HBC-6**	$CHCl_3$	6 days	92	92

[a] Conditions: **1a** = 0.4 mmol, **3** = 0.48 mmol, **HBC** = 0.08 mmol, and solvent = 2 mL. [b] Yield of the isolated product. [c] Determined by chiral HPLC. [d] The reaction was carried out at 0 °C. [e] The reaction was carried out at −40 °C for one day and −20 °C for five days. Mes = mesityl.

and various chiral HBCs efficiently facilitated the enantioselective intramolecular RC reaction of **1a**. To our delight, catalyst HBC-**6**, which is obtained from optically pure 1,2-diaminocyclohexane and 1,2-diphenylethylenediamine,[21] was identified as the optimal co-catalyst after extensive screening (Table 1, entry 6). No background reaction was observed with either **3** or HBC-**6** independently. Notably, the reaction exhibits complete chemoselectivity with this catalyst combination because the formation **4a** as another possible product was not observed. On this basis, a brief survey of the reaction media was performed. The RC reaction of **1a** worked very well in chloroform at −40 °C and afforded **2a** 92 % yield of the isolated product with 92 % *ee* (Table 1, entry 12).

Scope of the crossed Rauhut–Currier reaction: Experiments that probe the scope of substrates bearing two tethered activated alkenes are highlighted in Table 2. Gratifyingly, the reaction displays excellent generality, and significant structural variation in nitroolefin enoates **1a–l** can be realized. Typically, methyl and methoxy substituents can be incorporated on the benzene ring at the *meta* and/or *para* positions to the oxygen atom without loss of reaction efficiency or stereocontrol (Table 2, entries 2–4, 9, and 10: 83–97 % yield, 90–93 % *ee*). Moreover, substrates substituted with electron-deficient *para*-F, -Cl, or -Br atoms have been successfully utilized in this reaction with little influence on the reaction selectivity (Table 2, entries 5–7: 86–98 % yield, 91–93 % *ee*). It is of note that such halogenated products would be valuable synthons for the further construction of molecular complexity through transition-metal-catalyzed coupling technologies. As expected the sulfur-tethered substrate **1k** produces **2k** in 74 % yield with good enantiocontrol (Table 2, entry 11), employment of which would afford functionalized thiochromenes efficiently. Aliphatic substrates are also tolerated. For example, nitroolefin enoate **1l** underwent cyclization to give **2l** in moderate yield with good enantioselectivity (Table 2, entry 12). Note that the absolute configuration of the stereocenter in the 2*H*-chromene **2g** was unambiguously determined to be the *R* isomer by X-ray crystallographic studies,[22] and the stereochemistry of other products could be tentatively assigned by assuming an analogous enantioinduction (Figure 1).

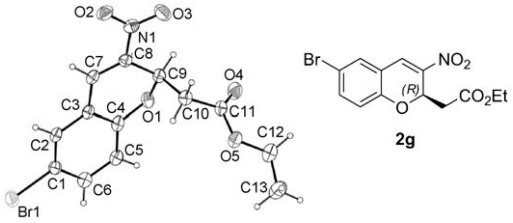
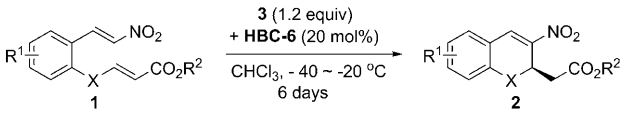
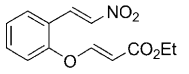
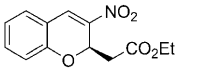
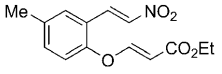
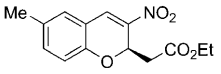
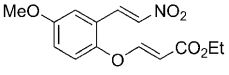
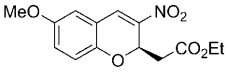
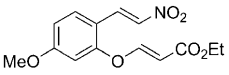
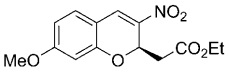
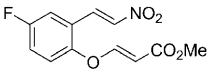
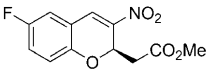
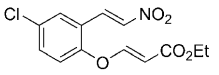
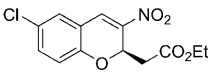
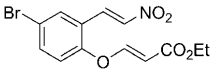
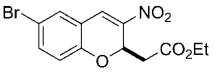
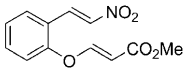
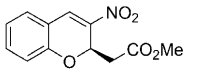
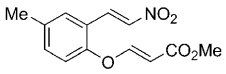
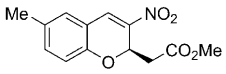
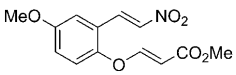
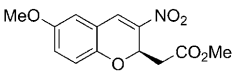
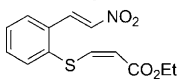
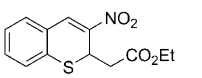
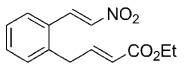
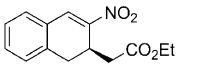


Figure 1. X-ray crystal structure of **2g**.

Table 2. Enantioselective intramolecular crossed Rauhut–Currier reactions of nitroolefin enoates.[a]

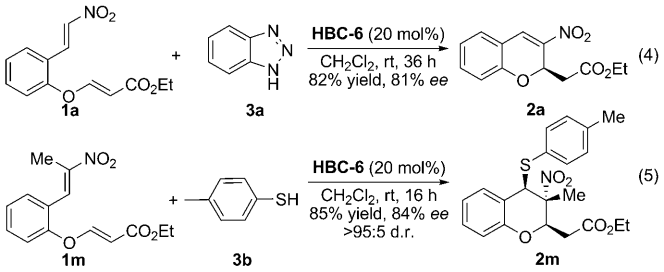


Entry	Nitroolefin	Product	Yield [%][b]	*ee* [%][c]
1	 **1a**	 **2a**	92	92
2	 **1b**	 **2b**	93	92
3	 **1c**	 **2c**	91	90
4	 **1d**	 **2d**	97	93
5	 **1e**	 **2e**	86	91
6	 **1f**	 **2f**	95	93
7[d]	 **1g**	 **2g**	98	91
8	 **1h**	 **2h**	87	98
9	 **1i**	 **2i**	83	91
10	 **1j**	 **2j**	85	90
11[e]	 **1k**	 **2k**	74	73
12[e]	 **1l**	 **2l**	52	73

[a] Conditions: **1a** = 0.4 mmol, **3** = 0.48 mmol, HBC = 0.08 mmol, and $CHCl_3$ = 2 mL at −40 °C for one day and −20 °C for five days. [b] Yield of the isolated product. [c] Determined by chiral HPLC. [d] The absolute configuration of **2g** was determined by X-ray studies.[22] [e] The reaction was carried out at 0 °C for one day and room temperature for five days.

Moreover, further extension of the scope of substrates in the present transformation has been successfully achieved. For example, the reaction of nitroolefin enoate **1a** with 1*H*-benzo[d][1,2,3]triazole (**3a**) worked very well in the presence of catalyst HBC-**6**, thus affording the corresponding

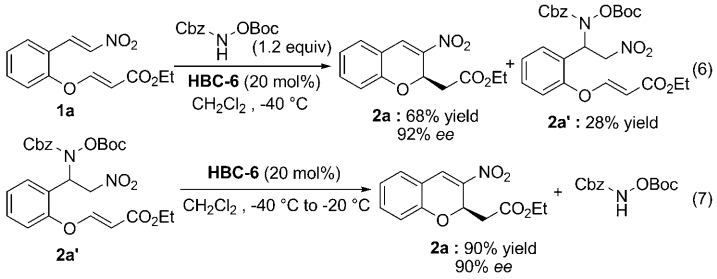
RC product **2a** in 82% yield with 81% *ee* [Eq. (4)]. Notably, when *para*-thiocresol (**3b**) acted as the nucleophilic promoter, the α-methyl-substituted nitroolefin enoate **1m** can also participate in this cascade reaction efficiently to provide the corresponding product **2m** in good yield (85%) with excellent stereoselectivity [84% *ee*, >95:5 d.r.; Eq. (5)].[18a]



(4)

(5)

Mechanistic investigation into the crossed Rauhut–Currier reaction: To investigate the proposed pathway of this RC reaction, the reaction was quenched after 3 days at −40 °C, and the desired RC product **2a** and aza-Michael addition reaction product **2a′** were obtained [Eq. (6)]. When **2a′** was treated under the standard conditions, it afforded RC product **2a** without erosion of the enantioselectivity [Eq. (7)]. Moreover, detailed computational studies were performed to understand the mechanism and enantioinduction of the reaction.



(6)

(7)

Computational studies were performed by using the Gaussian 03[23] program to investigate the proposed mechanism of the RC reaction (Scheme 2). Density functional theory (DFT) with the Becke three-parameter hybrid exchange functional and Lee-Yang-Parr correlation functional (B3LYP)[24] with the 6-31G-(d,p) basis set[25] were employed in the calculations. Modified **HBC-3–6** (with the inclusion of a thiourea and dimethyl-ring alkyl group and replacement of other groups by methyl groups; Table 1) were chosen as the hydrogen-bonding catalysts. Frequency calculations were performed at the same level of theory to obtain the values of the zero-point energy (ZPE), enthalpy, entropy, and Gibbs Free energy and to confirm the nature of the stationary points. Unless indicated otherwise, all the energy data discussed herein are for the Gibbs Free energy at room temperature (298.15 K) in the gas phase. The solvent effects were computed by using the polarizable continuum method (PCM; i.e., defaulted integral equation formalism (IEF) PCM (IEFPCM) method[26]) at the same level by using the gas-phase optimized structures, except for the initial reaction between the **HBC** and nucleophilic promoter (**NuP**), which was fully optimized (all the PCM calculations were performed in CH_2Cl_2 ($\varepsilon = 8.93$)).

A five-step reaction pathway was suggested for this reaction (Scheme 2 and Figure 2). Initially, the **NuP** is activated by the **HBC** through proton transfer from **NuP** to the tertiary amine of the **HBC**, thus affording the **NuP**$(-H)^-$/**HBC**$(H)^+$ complex.[27,28] DFT calculations show that the barrier energy of this step is so low (only 3.9 kcal mol^{-1} in the gas phase and 2.4 kcal mol^{-1} when the solvent effects are included) that this process should proceed very quickly. Following the proton transfer, a strong hydrogen bond is formed between the nitro group of the substrate and the quaternary ammonium group of **HBC**(H^+), therefore activating the LUMO of the unsaturated substrate. The nitrogen atom (N1) of the **NuP** is oriented by the thiourea group to attack the carbon atom (C1) of the substrate to provide **INT1**. The calculations predicted the same energy barrier (14.4 kcal mol^{-1}) of this step for both the *R* and *S* enantiomers and suggest that these two reactions compete with each other. The relative energies of **INT1** with regard to the *R* and *S* enantiomers were 2.0 and 3.7 kcal mol^{-1}, respectively, which indicate that the *R* enantiomer is more thermodynamically favorable. The subsequent intramolecular Michael addition reaction constructed a six-membered ring intermediate (**INT2**). The values for the relative Gibbs Free energy for the *R* and *S* enantiomers were $\Delta G = 16.1$ and 21.7 kcal mol^{-1}, and the energy barriers of this step were 14.1 and 18.0 kcal mol^{-1}, respectively. Whereas, the hydrogen atom (H1) transfers from the nitrogen atom (N3) of **HBC**(H^+) to the carbon atom (C4) of the enolate to form

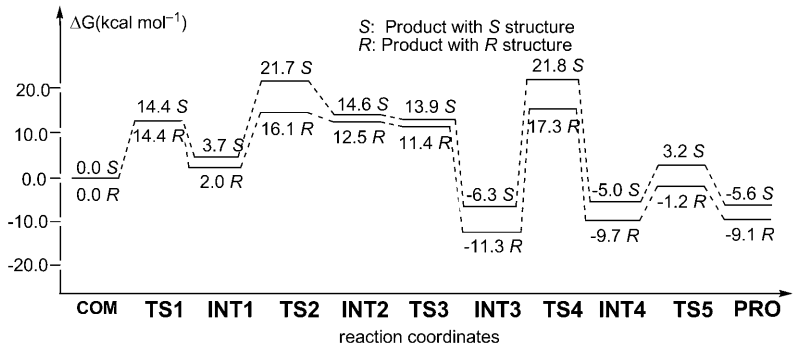
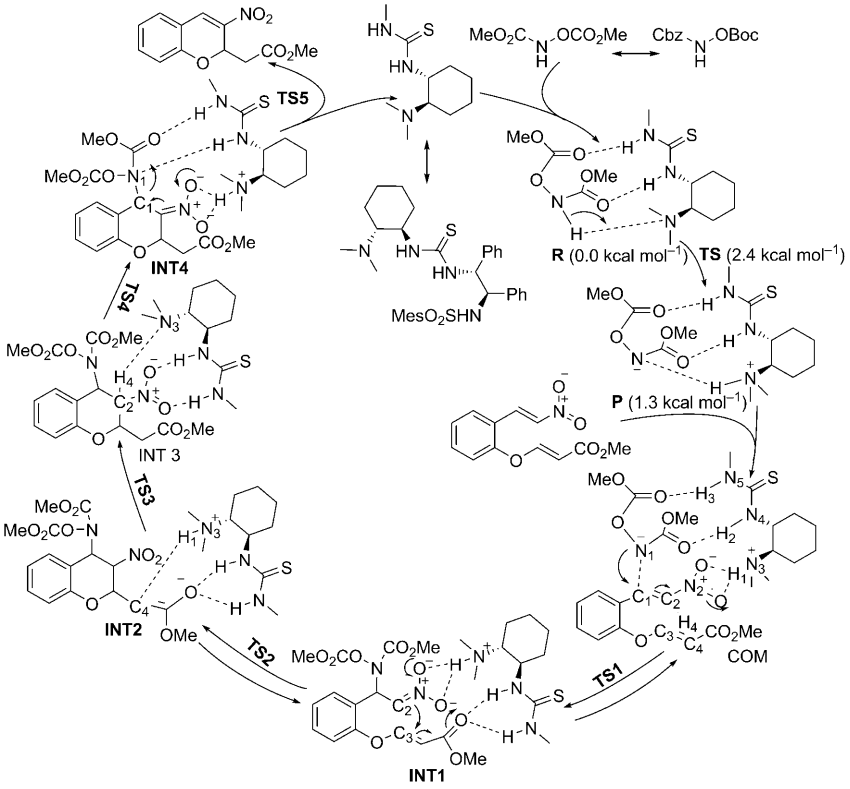


Figure 2. Profile of the Gibbs Free energy values for the RC reaction. **COM** = Complex, ΔG = relative Gibbs free energy, **PRO** = product.



Scheme 2. Proposed pathway for the Rauhut–Currier cyclization reaction. INT = intermediate, TS = transition state.

INT3. The energy barrier of this step was only 1.6 and 1.2 kcal mol^{-1} for the *R* and *S* configurations without the zero-point energy (ZPE) correlation. Note that the energy of **TS3** was lower than **INT2** when the ZPE is included, as shown in the Gibbs Free energy profile (Figure 2). Vibrational frequency calculations confirmed that **TS3** was a saddle point and the negative eigenvalues of *R* and *S* enantiomers are −754.7 and −406.1 i, respectively. The vibrational mode with the imaginary frequency corresponds to the movement of H1 between N3 and C3. The calculated energies indicate that the proton transfer proceeds very easily.[29] The elimination of the **NuP** is a two-step reaction: the H4 transfers from C2 to the tertiary amine N3 of the **HBC** followed by a *retro*-aza-Michael reaction. The values of the relative Gibbs Free energy of the transition states are $\Delta G =$ 17.3 and −1.2 kcal mol^{-1} for the *R* enantiomer and $\Delta G =$ 21.8 and 3.2 kcal mol^{-1} for the *S* enantiomer. The reaction barriers are 28.6 and 8.5 kcal mol^{-1} for the *R* enantiomer and 28.1 and 8.2 kcal mol^{-1} for the *S* enantiomer. The size of the energy barrier of the proton-transfer step suggests that it was the rate-determining step of this reaction, and it could also explain why the reaction was slow. Further investigation of the **TS4** of the *R* enantiomer showed that if a water molecule was included in the proton-transfer reaction, the reaction barrier would decrease to 17.1 kcal mol^{-1}.[27,30]

Understanding of origin of the enantioselectivity: The values of the Gibbs Free energy for the formation of the *R* enantiomer are all smaller than that of the corresponding *S* enantiomer (Figure 2). The largest energy difference of 5.6 kcal mol^{-1} between the *R* and *S* enantiomers occurs during the intramolecular Michael reaction (**TS2**). We calculated the energies of both the *R* and *S* configurations for **HBC**(H^+) and the remaining portion (**Sub**+**NuP**$^-$(−H)) separately for **TS2** to account for the enantioselectivity of this reaction (Figure 3). It was found that **HBC**(H^+) contributed to nearly half of the energy between the two enantiomers, thus indicating that the energy difference comes from the intermolecular steric effect of the **HBC**. The remaining energy originated from the difference in the strength of the hydrogen bond. The distances of 1.614 and 1.758 Å between the hydrogen of the quaternary ammonium group and the oxygen of the nitro group for the *R* and *S* enantiomers suggested that the former had a stronger hydrogen-bonding effect than the latter. These results indicate that the **HBC** was more suitable to catalyze the formation of the *R* enantiomer.

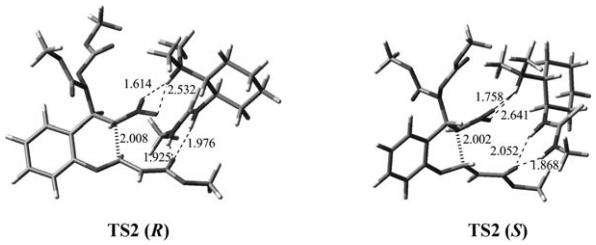
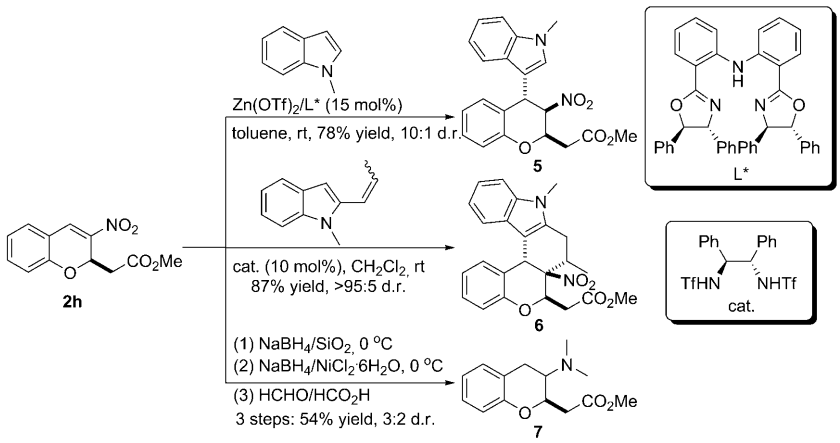


Figure 3. Structure of **TS2** and the energy gap of the separated part of **TS2** (distance in Å and energy in kcal mol^{-1}).

Derivatizations of the Rauhut–Currier reaction adduct: Perhaps more importantly, the enantio-enriched RC adducts can be readily transformed into biologically and pharmaceutically valuable compounds (Scheme 3). For example, the RC reaction product **2h** reacted with 1-methyl-1*H*-indole under the conditions developed by Xu and co-workers,[31] thus producing the highly functionalized indole-containing chroman derivative **5**. Furthermore, a formal [4+2] cycloaddition of **2h** to 2-propenylindole took place smoothly to generate the tetrahydrocarbazole derivative **6** in 87% yield of the isolated product with greater than 95:5 diastereoselec-



Scheme 3. Derivatizations of the Rauhut–Currier reaction adduct **2h**. Tf = trifluoromethyl.

tivity by using our recently developed strategy.[32] This architecture widely exists in various naturally occurring alkaloids and synthetic analogues of medicinal importance,[33] some of which can be potentially used as tumor-growth inhibitors and protein kinase C inhibitors.[34] Notably, trebenzomine analogue **7** can be easily synthesized in 54% overall yield through an operationally simple three-step procedure from **2h**,[35] thus indicating that potentially medicinal candidates can be readily accessed from simple starting materials.

Conclusion

We have developed a highly enantioselective crossed RC reaction of nitroolefins with tethered α,β-unsaturated esters by merging nucleophilic activation and hydrogen-bonding catalysis. The reaction itself features simple experimental procedures and is completely atom economical under benign conditions. The synthetic utility of the RC reaction products are documented by the production of biologically and pharmaceutically valuable compounds in highly diastereoselectivity. In addition, computational investigations led to a good understanding of the proposed mechanism, which indicates that the stereoselectivity of the RC reaction is determined by an intramolecular-Michael addition step and the rate-determining step is a *retro*-aza-Michael addition reaction. The configuration of the RC reaction product predicted by computational calculations is in good agreement with the experimental observations.

Experimental Section

Representative procedure: Nitroolefin enoate **1a** (0.4 mmol, 105 mg) was added to a vial containing HBC-**6** (0.08 mmol, 46 mg) and benzyl (*tert*-butoxycarbonyl)oxycarbamate (**3**; 0.48 mmol, 128 mg) in $CHCl_3$ (2 mL) at −40 °C. The resulting reaction mixture was stirred at −40 °C for 1 day and warmed to −20 °C. After the reaction was determined to be complete by TLC analysis, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 20:1 ~ 15:1) to give the pure product **2a** as a yellow oil (92%, 92% *ee*). $[\alpha]_D^{16} = 72.40$ ($c = 0.94$ in $CHCl_3$); HPLC (Chiralpak AD-H column, hexane/2-propanol = 95:5, 0.7 mL min^{-1}; $\lambda = 254$ nm, 25 °C, $t_1 = 18.92$ min, $t_2 = 21.10$ min); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (s, 1H), 7.43–7.34 (m, 1H), 7.30 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.04 (t, $J = 7.5$ Hz, 1H), 6.95 (d, $J = 8.2$ Hz, 1H), 6.04 (dd, $J = 9.4$, 3.5 Hz, 1H), 4.18 (m, 4.3 Hz, 2H), 2.86 (dd, $J = 15.1$, 9.4 Hz, 1H), 2.71 (dd, $J = 15.1$, 3.5 Hz, 1H), 1.27 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.81$, 152.63, 140.59, 134.35, 130.39, 129.30, 122.86, 117.68, 117.46, 69.65, 61.07, 37.70, 14.02 ppm; MS: *m/z*: 261.8 $[M+H]^+$; elemental analysis (%) calcd for $C_{13}H_{13}NO_5$: C 59.31, H 4.98, N 5.32; found: C 59.30, H 4.95, N 5.30.

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[1] For a review, see: a) C. E. Aroyan, A. Dermenci, S. J. Miller, *Tetrahedron* **2009**, *65*, 4069–4084; for pioneering studies, see: b) A. B. Baylis, M. E. D. Hillman, Celanese Corp. , Ger. Offen. DE 2155113, **1972**; *Chem. Abstr.* 1972, 77, 434174; c) K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815; d) M. M. Rauhut, H. Currier, American Cyanamid Co. , U.S. Patent 307499919630122, **1963**; *Chem. Abstr.* **1963**, *58*, 11224a.

[2] For a Lewis acid-catalyzed reaction, see: T. E. Reynolds, M. S. Binkley, K. A. Scheidt, *Org. Lett.* **2008**, *10*, 2449–2452.

[3] a) R. K. Thalji, W. R. Roush, *J. Am. Chem. Soc.* **2005**, *127*, 16778–16779; b) S. A. Frank, D. J. Mergott, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405; c) L.-C. Wang, A. L. Luis, K. Agapiou, H.-Y. Jang, M. J. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403; for a pioneering example of an intramolecular RC process, see: d) J. K. Ergüden, H. W. Moore, *Org. Lett.* **1999**, *1*, 375–377.

[4] For representative examples, see: a) W.-J. Yao, Y.-H. Wu, G. Wang, Y.-P. Zhang, C. Ma, *Angew. Chem.* **2009**, *121*, 9893–9896; *Angew. Chem. Int. Ed.* **2009**, *48*, 9713–9716; b) C. Zhong, Y.-F. Chen, J. L. Petersen, N. G. Akhmedov, X.-D. Shi, *Angew. Chem.* **2009**, *121*, 1305–1308; *Angew. Chem. Int. Ed.* **2009**, *48*, 1279–1282; c) N. T. McDougal, S. E. Schaus, *Angew. Chem.* **2006**, *118*, 3189–3191; *Angew. Chem. Int. Ed.* **2006**, *45*, 3117–3119; d) D. J. Mergott, S. A. Frank, W. R. Roush, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11955–11959; e) C. A. Evans, S. J. Miller, *J. Am. Chem. Soc.* **2003**, *125*, 12394–12395; f) D. G. Jellerichs, J.-R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 7758–7759.

[5] Although the RC reaction was first reported in 1963, there are few reports on the enantioselective variants to date; see: a) C. E. Aroyan, A. Dermenci, S. J. Miller, *J. Org. Chem.* **2010**, *75*, 5784–5796; b) C. E. Aroyan, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 256–257; c) F. Seidel, J. A. Gladysz, *Synlett* **2007**, 0986–0988; during the preparation of this report, Wu and co-workers developed the first example of a bifunctional phosphinothiourea-catalyzed enantioselective intramolecular Rauhut–Currier reaction of bis-enones, see:

d) J.-J. Gong, T.-Z. Li, K. Pan, X.-Y. Wu, *Chem. Commun.* **2011**, *47*, 1491–1493.

[6] J. Wang, H.-X. Xie, L.-S. Zu, W. Wang, *Angew. Chem.* **2008**, *120*, 4245–4247; *Angew. Chem. Int. Ed.* **2008**, *47*, 4177–4179.

[7] E. Marqués-López, R. P. Herrera, T. Marks, W. C. Jacobs, D. Könning, R. M. de Figueiredo, M. Christmann, *Org. Lett.* **2009**, *11*, 4116–4119.

[8] Despite the superior Michael acceptor ability of the nitroalkene and the well-documented synthetic utility of the nitro group; for selected reviews, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; b) N. Ono, *The Nitro Group in Organic Synthesis*,Wiley-VCH, New York, **2001**; to our knowledge, only one single example has been reported about the intramolecular RC-type reaction of nitroalkenes, see reference [7]).

[9] a) E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, **2008**; b) *Asymmetric Synthesis: The Essentials* (Eds.: M. Christmann, S. Bräse), Wiley-VCH, Weinheim, **2007**.

[10] a) H. C. Shen, *Tetrahedron* **2009**, *65*, 3931–3952; b) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2310; c) B. A. Keay in *Comprehensive Heterocyclic Chemistry II, Vol. 2* (Eds. A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, p. 395.

[11] S. J. Pastine, S. W. Youn, D. Sames, *Org. Lett.* **2003**, *5*, 1055–1058.

[12] a) C. Hardouin, L. Burgaud, A. Valleix, E. Doris, *Tetrahedron Lett.* **2003**, *44*, 435–437; b) P. Wipf, W. S. Weiner, *J. Org. Chem.* **1999**, *64*, 5321–5324; c) J. P. A. Harrity, D. S. La, D. R. Cefalo, M. S. Visser, A. H. Hoveyda, *J. Am. Chem. Soc.* **1998**, *120*, 2343–2351; d) J. P. A. Harrity, J. S. Wisser, J. D. Gleason, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 1488–1489.

[13] a) B. C. Das, S. Mohapatra, P. D. Campbell, S. Nayak, S. M. Mahalingam, T. Evans, *Tetrahedron Lett.* **2010**, *51*, 2567–2570; b) S.-P. Luo, Z.-B. Li, L.-P. Wang, Y. Guo, A.-B. Xia, D.-Q. Xu, *Org. Biomol. Chem.* **2009**, *7*, 4539–4546; c) P. Kotame, B.-C. Hong, J.-H. Liao, *Tetrahedron Lett.* **2009**, *50*, 704–707; d) K.-G. Liu, A. Chougnet, W.-D. Woggon, *Angew. Chem.* **2008**, *120*, 5911–5913; *Angew. Chem. Int. Ed.* **2008**, *47*, 5827–5829; e) H. Sundén, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* **2007**, *13*, 574–581; f) H. Li, J. Wang, T. E-Nunu, L.-S. Zu, W. Jiang, S.-H. Wei, W. Wang, *Chem. Commun.* **2007**, 507–509.

[14] For recent reviews, see: a) C. Zhong, X.-D. Shi, *Eur. J. Org. Chem.* **2010**, 2999–3052; b) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745–2755; c) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; e) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666–4683; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583.

[15] For selected examples, see: a) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986–990; b) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345–5347; c) S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628–13630; d) T. Yang, A. Ferrali, F. Sladojevich, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 9140–9141; e) C. Li, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967–6969; f) W.-H. Hu, X.-F. Xu, J. Zhou, W.-J. Liu, H.-X. Huang, J. Hu, L.-P. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782–7783; g) A. Duschek, S. F. Kirsch, *Angew. Chem.* **2008**, *120*, 5787–5789; *Angew. Chem. Int. Ed.* **2008**, *47*, 5703–5705; h) B.-Q. Zeng, X. Zhou, X.-H. Liu, X.-M. Feng, *Tetrahedron* **2007**, *63*, 5129–5136; i) I. Ibrahem, A. Córdova, *Angew. Chem.* **2006**, *118*, 1986–1990; *Angew. Chem. Int. Ed.* **2006**, *45*, 1952–1956; j) N. Yamagiwa, H. Qin, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13419–13427; k) G. M. Sammis, H. Danjo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 9928–9929; l) J. E. Imbriglio, M. M. Vasbinder, S. J. Miller, *Org. Lett.* **2003**, *5*, 3741–3743.

[16] L.-Q. Lu, Y.-J. Cao, X.-P. Liu, J. An, C.-J. Yao, Z.-H. Ming, W.-J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 6946–6948.

[17] For selected references, see: a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953; b) E. E. Schweizer, O. Meeder-Nycz in *Chromenes, Chromanones, and Chromones* (Ed.: G. P. Ellis), Wiley-Interscience, New York, **1977**.

[18] a) X.-F. Wang, Q.-L. Hua, Y. Cheng, X.-L. An, Q.-Q. Yang, J.-R. Chen, W.-J. Xiao, *Angew. Chem.* **2010**, *122*, 8557–8561; *Angew. Chem. Int. Ed.* **2010**, *49*, 8379–8383; b) L.-Q. Lu, F. Li, J. An, J.-J. Zhang, X.-L. An, Q.-L. Hua, W.-J. Xiao, *Angew. Chem.* **2009**, *121*, 9706–9709; *Angew. Chem. Int. Ed.* **2009**, *48*, 9542–9545.

[19] a) F. Pesciaioli, F. D. Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8831–8834; *Angew. Chem. Int. Ed.* **2008**, *47*, 8703–8706; b) J. Vesely, I. Ibrahem, G.-L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792–795; *Angew. Chem. Int. Ed.* **2007**, *46*, 778–781.

[20] See the Supporting Information for more details on optimization of the conditions and synthetic transformations.

[21] a) X.-Q. Dong, H.-L. Teng and C.-J. Wang, *Org. Lett.* **2009**, *11*, 1265–1268; b) C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431–1433; c) C.-J. Wang, X.-Q. Dong, Z.-H. Zhang, Z.-Y. Xue, H.-L. Teng, *J. Am. Chem. Soc.* **2008**, *130*, 8606–8607.

[22] The configuration of **2g** was determined by X-ray crystallographic analysis. CCDC-763160 (**2g**) contains the supplementary crystallographic data for 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.

[23] Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**..

[24] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.

[25] a) Y. Takano, K. N. Houk, *J. Chem. Theory Comput.* **2005**, *1*, 70–77; b) W. J. Hehre, L. Radom, P. v. R. Schleyer, J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, **1986** and references cited therein.

[26] a) M. T. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032–3037; b) B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *106*, 5151–5158; c) B. Mennucci, E. Cancès, J. Tomasi, *J. Phys. Chem. B* **1997**, *101*, 10506–10517; d) J. Tomasi, B. Mennucci, E. Cancès, *J. Mol. Struct. (Theochem)* **1999**, *464*, 211–226.

[27] See the Supporting Information for more details on the proton-transfer reaction between the **NuP** and **HBC**, the solvent effect (using the PCM model) to the RC reaction, and the influence of a water molecule on the **TS4**.

[28] A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

[29] L. Ding, W.-H. Fang, *J. Org. Chem.* **2010**, *75*, 1630–1636.

[30] For selected examples of how water accelerated the rate of reaction, see: a) J. J. Devery III, J. C. Conrad, D. W. C. MacMillan, R. A. Flowers II, *Angew. Chem.* **2010**, *122*, 6242–6246; *Angew. Chem. Int. Ed.* **2010**, *49*, 6106–6110; b) Y. Liang, H.-L. Zhou, Z.-X. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 17783–17785; c) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582–585; d) Y.-Z. Xia, Y. Liang, Y.-Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y.-H. Li, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3470–3471.

[31] S.-F. Lu, D.-M. Du, J.-X. Xu, *Org. Lett.* **2006**, *8*, 2115–2118.

[32] X.-F. Wang, J.-R. Chen, Y.-J. Cao, H.-G. Cheng, W.-J. Xiao, *Org. Lett.* **2010**, *12*, 1140–1143.

[33] For selected examples, see: a) H.-J. Knölker, R. R. Kethiri, *Chem. Rev.* **2002**, *102*, 4303–4428; b) C. J. Moody, *Synlett* **1994**, 681–688; c) N. Misra, R. Luthra, K. L. Singh, S. Kumar in *Comprehensive Natural Products Chemistry, Vol. 4* (Eds.: J. W. Kelly, D. Barton, K. Nakanishi, O. Meth-Cohn), Elsevier, Amsterdam, **1999**, p. 54; d) D. P. Chakraborty in *Progress in the Chemistry of Organic Natural Products, Vol. 34* (Eds.: W. Herz, H. Grisebach, G. W. Kirby), Springer-Verlag, Wien, **1977**, pp. 299–371.

[34] a) A. Nikitenko, D. Evrard, A. L. Sabb, R. L. Vogel, G. Stack, M. Young, M. Lin, B. L. Harrison, J. R. Potoski, *Org. Process Res. Dev.* **2008**, *12*, 76–80; b) A. L. Sabb, R. L. Vogel, G. P. Stack, D. A. Evrard, A. A. Failli, L. Krishnan, A. W. Chan, J. Ren, C. Guinosso, R. B. Baudy, J. Y.-C. Sze, Y. Li, C. J. Stanton III, A. Nikitenko, Wyeth Corp. , New Jersey, PCT Int. Appl. WO 2006/089053; *Chem. Abstr.* **2006**, *145*, 271641; c) B. Gopalan, H. V. Joshi, D. M. Shah, S. R. Ghorpade, Glenmark Pharm. Ltd., Mumbai, PCT Int. Appl. WO 2005/033099.

[35] M. Stanley, J. Rotrosen, N. Sculerati, S. Gershon, C. Kuhn, B. M. Cohen, *Psychopharmacology* **1979**, *66*, 23–27.

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