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Organocatalytic One-Pot Asymmetric Synthesis of 4*H*,5*H*-Pyrano[2,3-*c*]pyrazoles

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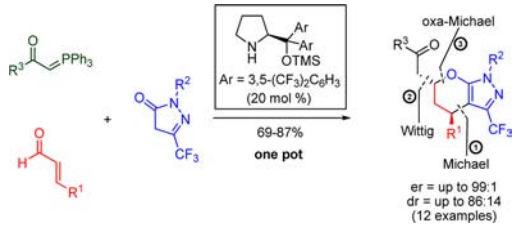
ABSTRACT



An efficient one pot asymmetric synthesis of tetrahydropyrano[2,3-*c*]pyrazoles has been developed. This class of biologically active heterocycles can be obtained via a secondary amine catalyzed asymmetric Michael/Wittig/oxa-Michael reaction sequence. Remarkably, the title compounds were accessible in good to very good yields and very good to excellent enantioselectivities after a single purification step.

Pyrazoles are one of the most important classes of bioactive heterocycles gaining increased interest from pharmaceutical, chemical, and agricultural industries over the past decade.[1] Among various possible pyrazole derivatives, pyrazolones have played an outstanding role for more than one century. As a matter of fact, in 1884 Knorr and Filehne developed phenazone (**1**), which is the very first fully synthetic antipyretic and analgesic,[2] sometimes also referred to as the "mother" of all modern painkillers,[3] while its successor metamizole (**2**) is the strongest antipyretic in modern medicine (Figure 1). Currently, many pyrazole and pyrazolone derivatives are known with a broad range of bioactive properties such as anti-inflammatory, antipyretic, analgetic, antiviral, antibacterial, antifungal, etc. Furthermore, they are used in food and chemical industries as optical bleach, food colorants, and ligands for transition metals.[1]

After the first synthesis of a pyrazole derivative in 1883[4] and one year later of pyrazolone,[5] much effort was focused toward developing new preparation methods for these heterocycles, usually via condensation of dicarbonyl compounds with hydrazines or [3+2]-cycloadditions, and their subsequent derivatization.[6]

Due to tautomerism, 5-hydroxy-1,2-diazoles can act either as a carbonyl compound or as an aromatic heterocycle. In solution the pyrazolone form predominates leading to carbonyl reactivity while an appreciable amount of the aromatic pyrazole-5-ol is only present in the case of a special substitution pattern.[7] Several alkylations of

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(4) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2597–2599.
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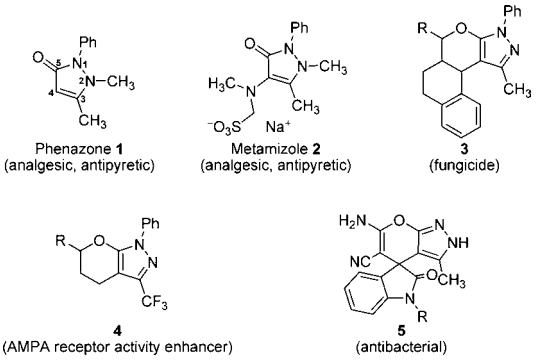


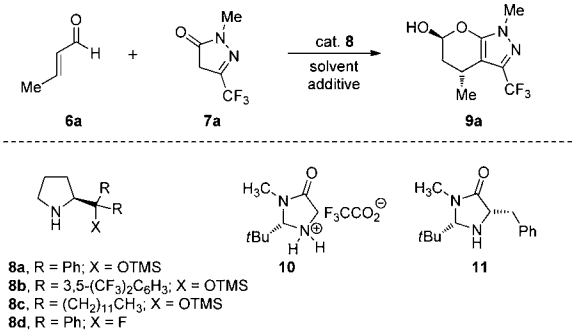
Figure 1. Bioactive pyrazolones and tetrahydropyrano[2,3-*c*]-pyrazoles.

pyrazolones α to the carbonyl group have been reported,[8] but only a few were performed in an enantioselective manner.[9] Herein the pyrazolones acted as typical enolates; no aromatization was observed, and therefore after the first alkylation in the α-position a second alkylation could take place. In contrast, Friedel–Crafts-type alkylations of pyrazole-5-ols are possible when the aromatic form is stabilized by an electron-withdrawing group (e.g., a trifluoromethyl group in the 3-position or carbonyl group in the 4-position),[10] but to the best of our knowledge, there are no reports of performing this reaction in an enantioselective fashion.

Hence we would like to close this gap and report the first asymmetric synthesis of tetrahydropyrano[2,3-*c*]pyrazoles in one pot via a Michael/acetalization cascade followed by a ring-opening/Wittig/oxa-Michael domino reaction. The core structure of the corresponding products is present in several bioactive molecules[11] (Figure 1, compounds **3**–**5**).

We started our investigations by optimizing the reaction conditions of the Michael/acetalization cascade reaction

Table 1. Optimization of the Reaction Conditions[a]



entry	cat. (mol %)	solvent	additive (mol %)	yield[b] (%)	er[c]
1	**8a** (2.5)	$CHCl_3$	–	76	80:20
2	**8b** (2.5)	$CHCl_3$	–	88	83:17
3	**8c** (2.5)	$CHCl_3$	–	22	76:24
4	**8d** (2.5)	$CHCl_3$	–	88	70:30
5	**10** (2.5)	$CHCl_3$	–	97	55:45
6	**11** (2.5)	$CHCl_3$	–	45	67:33
7	**8b** (2.5)	CH_2Cl_2	–	82	83:17
8	**8b** (2.5)	Toluene	–	94	83:17
9	**8b** (2.5)	$CHCl_3$	AcOH (10)	80	77:23
10	**8b** (2.5)	$CHCl_3$	BZA (10)	71	77:23
11	**8b** (2.5)	$CHCl_3$	pNO_2-BZA (10)	88	77:23
12	**8b** (2.5)	$CHCl_3$	TsOH (10)	n.r.	–
13[d]	**8b** (20)	**Toluene/ MeOH (10:1)**	–	**95**	**89:11**

[a] Reaction conditions: **6a** (1.0 mmol), **7a** (1.0 mmol), solvent (4.0 mL), 24 h, rt, under air. [b] Yields of **9a** were determined via ^{1}H NMR spectroscopy using 4,4′-di-*tert*-butylbiphenyl (DTBP) as internal standard; sum of isomers. [c] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase after converting **9a** to **13k**. [d] At −78 °C. *p*TsOH = *p*-toluenesulfonic acid. BZA = benzoic acid.

utilizing 3-trifluoromethylpyrazolone **7a** and crotonaldehyde (**6a**) in the presence of diphenyl TMS-prolinol **8a** (Table 1). Indeed the reaction proceeded smoothly in chloroform affording the acetal **9a** in 76% yield. Unfortunately, rapid equilibrium between the two diastereomers (dr 71:29) and the open chained form of **9a**[12] and its instability at higher temperature prevented the determination of the enantiomeric ratio of **9a** by HPLC or gas chromatography. Hence, **9a** was treated with a Wittig reagent **12** leading to configurationally stable tetrahydropyrano[2,3-*c*]pyrazoles **13** via a spontaneous ring-opening/Wittig/oxa-Michael domino reaction (scheme in Table 2). Best results were achieved in toluene or chlorinated solvents at rt yielding compounds **13** in 85–86% yields and moderate diastereoselectivities (dr 71:29).[13]

After having established this protocol we continued the optimization of the conditions of the Michael/acetalization cascade reaction applying different catalysts. The MacMillan imidazolidinone **10** showed the best product

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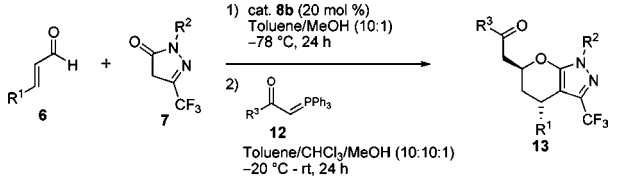
(10) For selected examples, see: (a) Wong, F. F.; Huang, Y.-Y. *Tetrahedron* **2011**, *67*, 3863–3867. (b) Abaszadeh, M.; Sheibani, H.; Saidi, K. *Aust. J. Chem.* **2010**, *63*, 92–95. (c) Guo, C.; Holzer, W. *Molbank* **2009**, M605. (d) Castognolo, D.; De Logu, A.; Radi, M.; Bechi, B.; Manetti, F.; Magnani, M.; Meleddu, R.; Chisu, L.; Botta, M. *Bioorg. Med. Chem.* **2008**, *16*, 8587–8591. (e) Yao, C.-S.; Yu, C.-X.; Tu, S.-J.; Shi, D.-Q.; Wang, X.-S.; Zhu, Y.-Q.; Yang, H.-Z. *J. Fluorine Chem.* **2007**, *128*, 105–109. (f) Bol'But, A. V.; Dorokhov, V. I.; Sukach, V. A.; Tolmachev, A. A.; Vovk, M. V. *Russ. J. Org. Chem.* **2003**, *39*, 1860–1862. (g) Ceulemans, E.; Voets, M.; Emmers, S.; Uytterhoeven, K.; Meervelt, L. V.; Dehaen, W. *Tetrahedron* **2002**, *58*, 531–544.

(11) (a) Stegelmeier, H.; Brandes, W. Bayer AG, U.S. Patent 4,515,801, May 7, 1985. (b) Mochizuki, M.; Imaeda, T. Takeda Pharmaceutical Company Limited, Int. Patent WO/2010/140339, Dec. 9, 2010. (c) Van Herk, T.; Brusee, J.; van den Nieuwendijk, A. M. C. H.; van der Klein, P. A. M.; IJzerman, A. P.; Stannek, C.; Burmeister, A.; Lorenzen, A. J. *Med. Chem.* **2003**, *46*, 3945–3951.

(12) The ratio between the closed and open chained form of **9a** was 88:12 as determined by ^{1}H NMR spectroscopy.

(13) For details on the optimization of the ring opening/Wittig/oxa-Michael cascade, see Supporting Information.

Table 2. Scope of Aldehyde and 3-Trifluoromethyl Pyrazolone[a,b]



13	R^1	R^2	yield[c] (%)	dr[d]	er[d] (*trans*)	er[d] (*cis*)
a	Me	Me	86	72:28	96:4	96:4
b	Me	Ph	85	71:29	94:6	93:7
c	Et	Me	73	77:23	97:3	98:2
d	*n*Pr	Me	77	79:21	98:2	99:1
e	*i*Pr	Me	70	64:36[e]	97:3	98:2
f	Ph	Me	88	64:36	88:12	n.d.
g	Bn	Me	81	86:14	97:3	99:1
h	CH_2OTIPS	Me	74	74:26	98:2	99:1
i	CH_2OBz	Me	84	84:16	96:4	n.d.
j	Bn	Ph	75	83:17[e]	98:2	93:7

[a] Reaction conditions: **6** (1.0 mmol), **7** (1.0 mmol), toluene/MeOH (4.0 mL), 24 h at −78 °C, then **12** (0.95 mmol), $CHCl_3$ (4.0 mL), 24 h at −78 to rt, under air. [b] R^3 was 3-(MeO)C_6H_4 for **13a**−**i** and 4-BrC_6H_4 for **13j**. [c] Yields of isolated diastereomeric mixture of **13**. [d] Diastereomeric and enantiomeric ratios were determined via HPLC analysis on a chiral stationary phase. [e] Diastereomeric ratio was determined via ^{1}H NMR spectroscopy. n.d. = not determined.

yield from all tested catalysts but with low asymmetric induction (Table 1, entry 5). A sterically more demanding catalyst **11** increased the enantiomeric ratio of the products, but the yields dropped significantly (Table 1, entry 6). Better results were achieved with prolinol derivatives **8a**−**8d** (Table 1, entries 1−4) with secondary amine **8b** performing the best and affording the desired product in 88% yield with a moderate enantiomeric ratio (83:17). Subsequently, a range of solvents and additives were tested. In all polar solvents the reaction was not clean giving only low yields (32−44%) while maintaining moderate enantiomeric ratios (er 66:34−76:24).[14] Similarly, the use of protic acids as additives in most cases did reduce both the yield and the enantiomeric ratios (Table 1, entries 9−12).[15] In contrast, toluene or dichloromethane improved both yields and enantioselectivities (Table 1, entries 7−8). Finally, by decreasing the temperature to −78 °C, increasing the catalyst loading to 20 mol %, and adding some methanol to toluene for better pyrazolone solubility we achieved excellent yields and good enantioselectivity in this reaction (Table 1, entry 13).

Recently, one-pot reactions have received a lot of attention since they reduce the number of purification steps, time, and costs and sometimes have a higher efficiency than the corresponding stepwise protocols.[16] With both steps toward the configurationally stable cascade product **13** optimized, we compared the results from the one-pot process and the stepwise protocol. Indeed, the first proved to be superior in yield (87% vs 83%; over two steps) and asymmetric induction (er 96:4 vs 89:11; major diastereomer) for compound **13k**. Therefore, the substrate scope was studied on the total asymmetric one-pot Michael/Wittig/oxa-Michael reaction sequence (Table 2). Different aldehydes and pyrazolones were applied yielding the desired one-pot products in good to very good yields and enantioselectivities with moderate diastereoselectivities. Aromatic aldehydes performed similar to aliphatic ones in terms of yield but with significantly lower enantiomeric excesses (Table 2, entry **13a** vs **13f**). Furthermore, branched aldehydes (Table 2, **13e**) and functional groups such as an ester or protected alcohol in the form of a silyl ether were tolerated (Table 2, **13h** and **13i**). Worth mentioning is that er values up to 98:2 were reached. Finally, more electron-rich 3-trifluoromethylpyrazolones bearing a phenyl moiety at the nitrogen atom were used without any loss in yield or selectivities (Table 2, **13b**). The configuration of the major diastereomer was trans, as was determined via NOESY experiments on compounds **13e** and **13f**. In addition, X-ray crystallographic analysis of compound **13j** confirmed the (4*R*,6*S*)-configuration (Figure 2).

Subsequently, we studied the influence of different phosphoranes on the reaction (Table 3). Electron-rich or -neutral Wittig reagents showed similar results leading to tetrahydropyrano[2,3-*c*]pyrazoles **13** in very good yields and enantioselectivities (Table 3, **13a** and **13k**). In contrast, less reactive phosphoranes bearing slightly electron-deficient substituents gave only moderate yields and good stereoinduction (Table 3, **13l**). Since the Wittig reagent cannot influence the stereogenic center generating step directly, there is likely a slow racemization and decomposition process present.[17] Hence, the faster the Wittig reagent can remove the intermediate acetal **9** from the reaction mixture by the formation of pyrazole derivative **13**, the higher the enantioselectivity and yield are. Finally, after changing group R^3 on the Wittig reagent from a ketone to an ester, cyclization was no longer observed leading to open-chained pyrazole-5-ol derivative **13m′**. Interestingly, the corresponding pyrazolone tautomer was not observed, while the product was isolated in very good yields.

The proposed mechanism of the reported cascade reaction is shown in Scheme 1. The reaction starts with the formation of the iminium intermediate **I** by condensation of the catalyst **8b** with the aldehyde **6**. The pyrazolone **7**

(14) For details on solvent screening, see Supporting Information.

(15) It is widely accepted that protic additives increase the reaction rate of secondary amine catalyzed reactions by providing a faster iminium ion formation. For a recent review, see:Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264.

(16) For a recent review on one-pot processes, see: Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem.* **2011**, *123*, 8642–8660. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492–8509.

(17) The slow decomposition of the intermediate acetal was proven by stirring an isolated and purified sample of **9a**, which initially had an er of 88:12, with (*R*)-**8a** as the catalyst in toluene/methanol 10:1 at rt. After 24 h the er dropped to 75:25 while more than 50% of the starting material decomposed. For details, see Supporting Information.

(18) CCDC-890616 contains the supplementary crystallographic data for the compound **13j** 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.

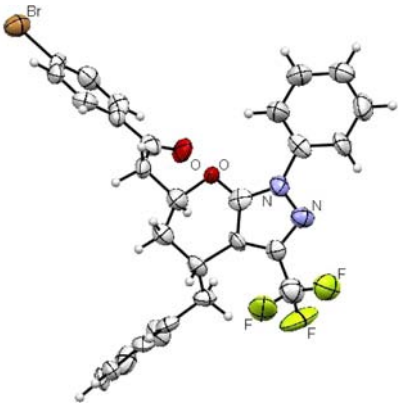
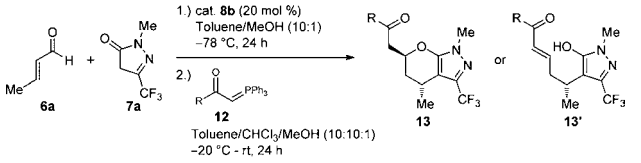


Figure 2. ORTEP plot of **13j** determined by X-ray analysis.[18]

Table 3. Influence of the Wittig Reagent[a]



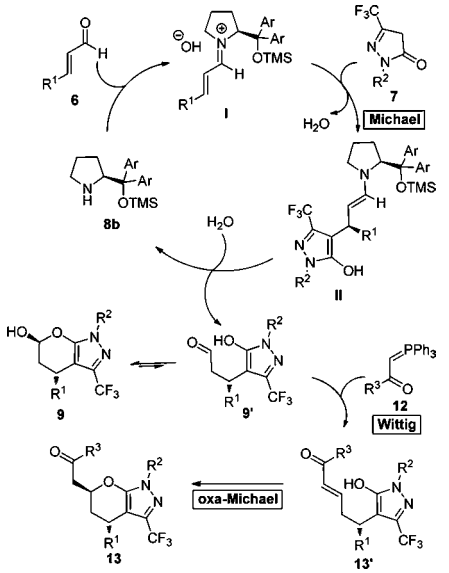
13	R	yield[b] (%)	dr[c]	er[c] (major)	er[c] (minor)
13a	3-(MeO)C_6H_4	86	72:28	96:4	96:4
13k	Ph	87	72:28	96:4	98:2
13l	4-BrC_6H_4	69	72:28	94:6	94:6
13m′	OEt	85	–	n.d.	n.d.

[a] Reaction conditions: see Table 2. [b] Yields of isolated diastereomeric mixture of **13** or of pure **13′**. [c] Diastereomeric and enantiomeric ratios were determined via HPLC analysis on a chiral stationary phase.

attacks the intermediate **I** from the backside generating the heteroaromatic structure **II**.[19] Subsequently, the catalyst **8b** is liberated by hydrolysis of **II** generating the intermediate **9** after hemiacetalization. Since compound **9** is in equilibrium with its open chained form **9′** the Wittig olefination occurs leading to the α,β-unsaturated

(19) We conclude that the aromatization occurs directly after or during the alkylation since in all isolated structures bearing a substituent in the 4-position such as **9** or **13′** the aromatic form was preferred. In contrast, the aromatic tautomer of pyrazolone **7** was not observed under our reaction conditions as was verified in a control experiment.

Scheme 1. Proposed Mechanism of the One-Pot Reaction Sequence



intermediate **13′**. Finally, spontaneous intramolecular oxa-Michael addition closes the ring to the final product **13**.

In summary, we have developed a new efficient asymmetric synthesis of tetrahydropyrano[2,3-*c*]pyrazoles. This class of biologically important compounds was accessible via a one-pot, asymmetric Michael/Wittig/oxa-Michael reaction sequence in very good yields and enantioselectivities. Noteworthy, the pyrazole derivative **9** formed as an intermediate is the formal product of a, thus far, unknown asymmetric Friedel–Crafts-type alkylation of pyrazole-5-ols.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.