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Asymmetric Squaramide Catalyzed Domino aza-Friedel-Crafts/N,O-Acetalization Reactions Between 2-Naphthols and Pyrazolinone Ketimines

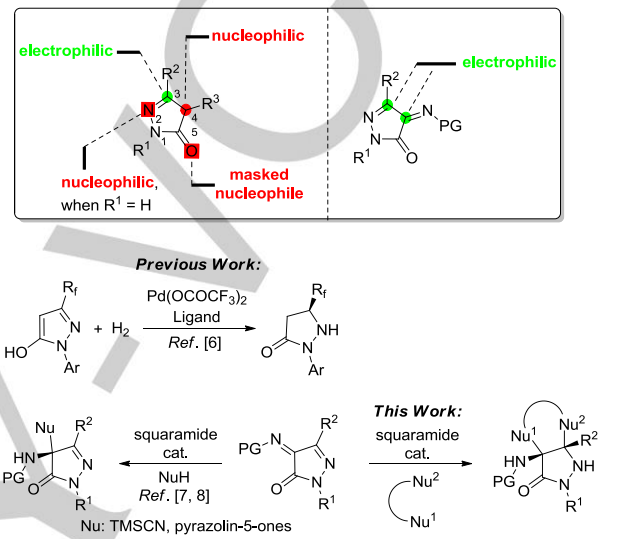
Uğur Kaya, Pankaj Chauhan*, Suruchi Mahajan, Kristina Deckers, Arto Valkonen, Kari Rissanen and Dieter Enders*

Dedicated to Professor Dieter Seebach on the occasion of his 80th birthday

Abstract: Pyrazolin-5-one derived *N*-Boc ketimines have been explored to develop an unprecedented domino aza-Friedel-Crafts/N,O-acetalization reaction with 2-naphthols. The novel protocol requires only a catalyst loading of 0.5 mol% of a bifunctional squaramide catalyst, is scalable to gram amounts, and provides a new series of furanonaphthopyrazolidinone derivatives bearing two vicinal tetra-substituted stereogenic centers in excellent yields (95-98%) and stereoselectivities (>99:1 dr and 97-98% *ee*). A different reactivity was observed in the case of 1-naphthols and other electron-rich phenols, which led to the aza-Friedel-Crafts adducts in 70-98% yield and 47-98% *ee*.

Among the nitrogen containing heterocycles pyrazole derivatives are a privileged class of compounds possessing a broad spectrum of applications as pharmaceutical and agrochemical products, photographic couplers and chelating agents in coordination chemistry.[1] In particular, the pyrazolin-5-one derivatives are very interesting aza-heterocycles bearing multiple reactive sites (Scheme 1).[2] The N-1,[3] C-4 [4] and 5-OH[5] positions at the pyrazolin-5-one are nucleophilic and these reactivities have been widely explored for the synthesis of new classes of enantiopure pyrazoles and pyrazolone derivatives. However, the use of pyrazolin-5-ones for the asymmetric synthesis of pyrazolidinones is not well documented. In this context, Zhou's group recently identified the rare reactivity of the pyrazolin-5-ones, where the C-3 position bearing a trifluormethyl group acts as an acceptor of hydride to afford pyrazolidinone derivatives.[6] On the other hand, recently our group reported the development of a new class of ketimines derived from pyrazolin-5-ones and utilized its C-4 electrophilicity to develop an enantioselective Strecker reaction[7] and pyrazolin-5-one Mannich-type[8] additions. The C-3 and C-4 electrophilic reactivities of pyzazolin-5-one derived ketimines, however, are not fully exploited.

We envisioned that by using a substrate with two nucleophilic centers such as naphthols[9], a double addition to the ketimine derived from pyrazolin-5-one can take place via a domino reaction[10]. This kind of aza-Friedel-Crafts/N,O-acetalization domino sequence may lead to the formation of a new series of enantiopure dihydronaphthofurans bearing a pyrazolidinone scaffold with two vicinal tetra-substituted stereocenters.



Scheme 1. Reactivity of pyrazolones and pyrazolone derived *N*-Boc ketimines.

It is important to mention that dihydronaphthofuran and pyrazolidinone scaffolds are the core structures of many natural and synthetic bioactive compounds (Figure 1)[11]. Owning to the wide application of these heterocyclic molecules, several synthetic methods have been developed to procure these classes of compounds.[12] Surprisingly, only a few asymmetric methods are available to construct enantiopure dihydronaphthofuran[13] and pyrazolidinone derivatives.[14]

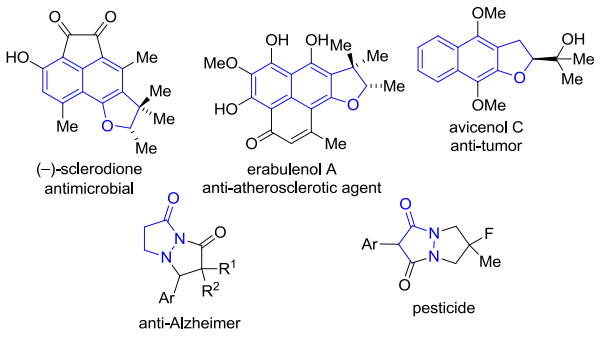


Figure 1. Bioactive natural products and synthetic compounds bearing a dihydronaphthofuran or a pyrazolidinone scaffold.

Herein we report a new organocatalytic asymmetric domino aza-Friedel-Crafts/N,O-acetalization reaction between 2-naphthols **1** and ketimines **2** derived from pyrazolin-5-ones to provide furanonaphthopyrazolidinone derivatives **3**. Firstly, we investigated the reaction between 2-naphthol (**1a**) and *N*-Boc ketimine **2a** in the presence of various thiourea[15] and

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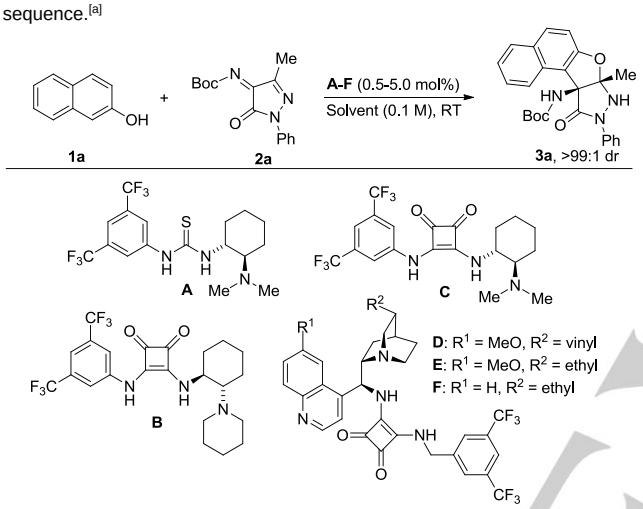
squaramide[16] catalysts (Table 1). The initial reaction was carried out with the thiourea catalyst **A** and resulted in the formation of a single diastereomer of the desired furanonaphthopyrazolidinone **3a** *via* an aza-Friedel-Crafts/N,O-acetalization reaction in 98% yield and 65% *ee* (entry 1). The squaramide **B** catalyst provided the product **3a** with excellent yield with an increase in the *ee*-value to 90% (entry 2). We then extended the catalyst screening by using other squaramide catalysts **C**-**F** (entries 3-6). In the corresponding reactions excellent results could be achieved in terms of product yields and enantioselectivities. The catalyst **D** was then chosen for further optimization studies for the aza-Friedel-Crafts/N,O-acetalization reaction.

Table 1. Optimization of the domino aza-Friedel-Crafts/N,O-acetalization sequence.[a]

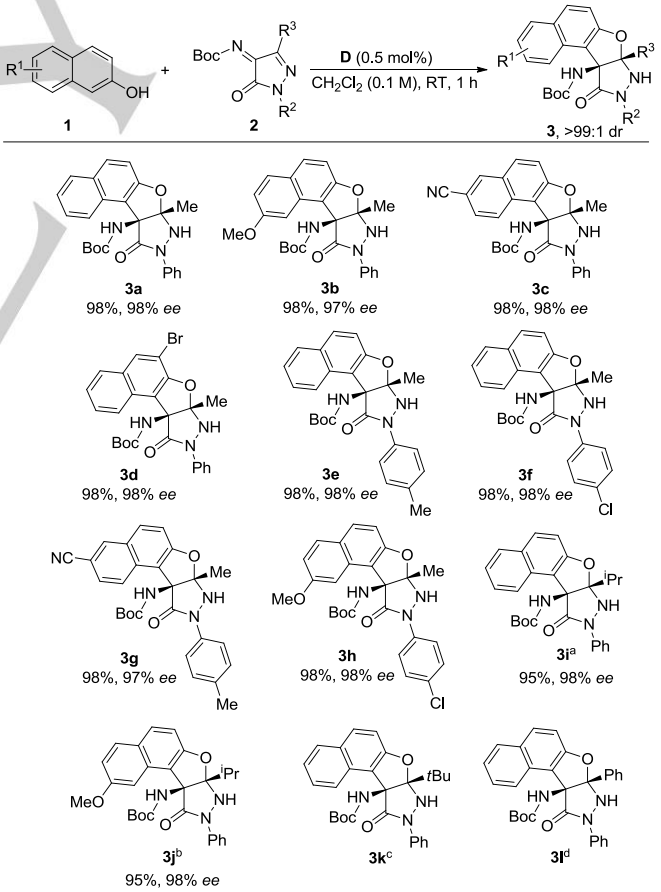


Entry	Catalyst	Solvent	Reaction time	Yield [%][b]	*ee* [%][c]
1[d]	**A**	CH_2Cl_2	20 min	98	65[e]
2	**B**	CH_2Cl_2	30 min	98	90
3	**C**	CH_2Cl_2	30 min	98	97[e]
4	**D**	CH_2Cl_2	25 min	98	99
5	**E**	CH_2Cl_2	25 min	98	99
6	**F**	CH_2Cl_2	25 min	98	99
7	**D**	Toluene	3 h	98	96
8	**D**	Et_2O	22 h	82	98
9	**D**	$CHCl_3$	10 min	98	98
10[f]	**D**	CH_2Cl_2	30 min	98	99
11[g]	**D**	CH_2Cl_2	1 h	98	98

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.22 mmol, 1.1 eq.), **cat.** (5.0 mol%), solvent (2.0 mL, 0.1 M). [b] Yield of **3** after flash chromatography. [c] Determined by HPLC using a chiral stationary phase. [d] Carried out with 10 mol% of catalyst **A**. [e] The opposite enantiomer was obtained. [f] Carried out with 1 mol% catalyst **D**. [g] Carried out with 0.5 mol% of catalyst **D**.

Further investigations were carried out by screening other solvents. In toluene the reaction occurred with a slow rate with unchanged excellent yield and *ee*-value (entry 7), whereas in Et_2O as solvent a decrease in yield to 82% with a significant negative effect on the reaction rate was observed. In contrast to these results, the reaction in $CHCl_3$ was finished after 10 minutes with excellent yield and enantioselectivity (entry 9). Due to the higher toxicity of $CHCl_3$, CH_2Cl_2 was chosen for further optimization. Next, the catalyst loading of **D** was reduced to 1 mol% and the excellent results were obtained in 30 minutes. Even 0.5 mol% of the squaramide **D** was sufficient for this reaction to be completed in 1 hour with excellent yield and enantioselectivity (entry 11).

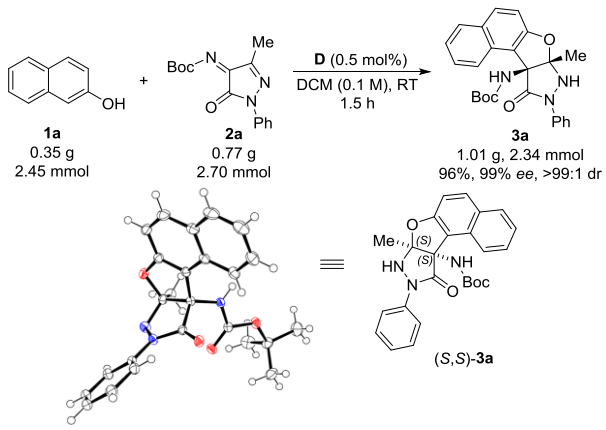
With the optimized conditions in hand (0.5 mol% of catalyst **D** in CH_2Cl_2), the substrate scope for the aza-Friedel-Crafts/N,O-acetalization reaction was investigated. The reaction of differently substituted 2-naphthols **1** with *N*-Boc ketimine **2a** provided the desired products **3a**-**d** with virtually complete diastereoselectivity in excellent yields and enantioselectivities (Scheme 2). Using *N*-Boc ketimines with different aryl groups at the N-1 position the excellent results in terms of yield and *ee*-values of **3e**-**h** could be maintained (Scheme 2). The methyl group as R^3 substituent of **2** could be successfully replaced by an isopropyl group resulting in the corresponding tetracyclic products **3i**-**j** in excellent yields and stereoselectivities. However, in the reaction with *N*-Boc ketimine bearing a *tert*-butyl group at



Scheme 2. Substrate scope with 2-naphthol. General reaction conditions: **1** (0.20 mmol), **2** (0.22 mmol, 1.1 eq.), **D** (0.5 mol%), CH_2Cl_2 (2.0 mL, 0.1 M). [a] Reaction time of 2 h. [b] Reaction time of 1.5 h. [c] Product formation was not observed. [d] With best of our effort, the compound **3l** could not be purified.

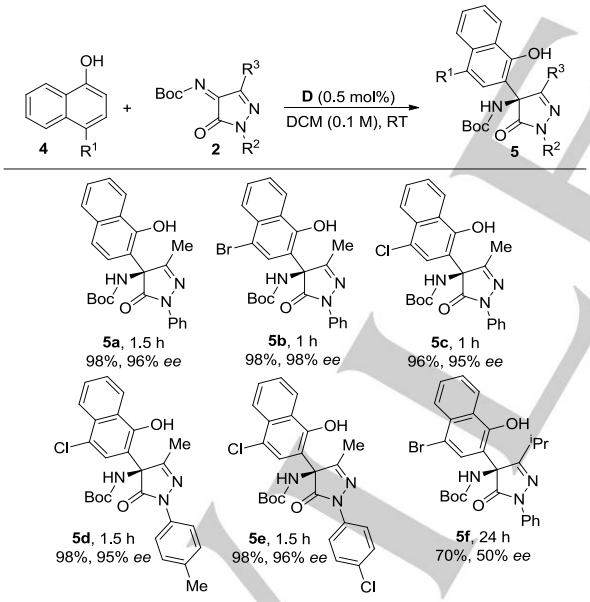
the C-3 position the desired product **3k** could not be observed, probably due to the higher steric hindrance. In the case of a phenyl group at the same position a product formation was noticed, but the purification of **3l** proved to be very difficult.

To demonstrate the synthetic efficiency and utility of the aza-Friedel-Crafts/N,O-acetalization sequence, we carried out a scale up reaction to prepare a gram amount of **3a** in excellent yield and stereoselectivity (Scheme 3).



Scheme 3. Scale-up synthesis and X-ray crystal structure of **3a**.

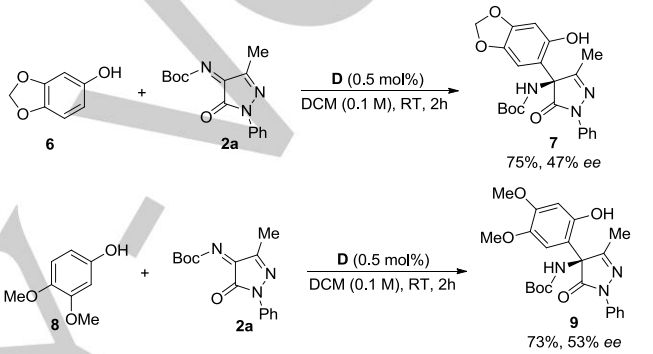
The absolute configuration of the furanonaphthopyrazolidinone products **3a-j** could be assigned as (*S*,*S*) analogy to the X-ray crystallographic analysis of compound **3a** (Scheme 3)[17].



Scheme 4. Substrate scope with 1-naphthol. General reaction conditions: **4** (0.20 mmol), **2** (0.22 mmol, 1.1 eq.), **A** (0.5 mol%), DCM (2.0 mL, 0.1 M).

It was expected that 1-naphthols **4** should also react with *N*-Boc-ketimines **2** *via* an aza-Friedel-Crafts/N,O-acetalization sequence to provide the corresponding tetracyclic products. However, in the reaction with 1-naphthol only the aza-Friedel-Crafts reaction was observed and the corresponding pyrazolone derivative **5a** was obtained in excellent yield and enantioselectivity (Scheme 4). With this interesting results in hand we studied the substrate scope of the reaction. Differently substituted 1-naphthols **4** and ketimines **2** derived from pyrazolin-5-ones were tolerated giving excellent yields and *ee*-values of **5a-f** (Scheme 4). Although the exact reason for this diverse reactivity is not known yet, a possible explanation may be the different rotation barriers around the carbon-carbon bond after the aza-Friedel-Crafts reaction of the 2-naphthol and the 1-naphthol.

To expand the scope of the method, electron-rich phenols[18] such as sesamol (**6**) and 3,4-dimethoxyphenole (**8**) were tested with the *N*-Boc ketimine **2a** under the optimized reaction conditions. The corresponding pyrazolone derivatives **7** and **9** could be obtained in moderate yields and enantioselectivities (Scheme 5).



Scheme 5. Substrate scope with electron-rich phenols. General reaction conditions: **6/8** (0.20 mmol), **2a** (0.22 mmol, 1.1 eq.), **D** (0.5 mol%), CH_2Cl_2 (2.0 mL, 0.1 M).

In conclusion, we have developed a squaramide catalyzed asymmetric domino aza-Friedel-Crafts/N,O-acetalization reaction between 2-naphthols and *N*-Boc ketimines of pyrazolinones to provide furanonaphthopyrazolidinone derivatives bearing two vicinal tetra-substituted stereogenic centers in excellent yields and stereoselectivities. A different reaction pathway was observed in the case of 1-naphthols or electron-rich phenols, which allowed a direct access to amino-pyrazolone derivatives *via* the aza-Friedel-Crafts reaction. The new protocols required only a sub-mol% of squaramide catalyst loading to achieve excellent stereocontrol in a short reaction time.

Experimental Section

The cinchona-derived squaramide catalyst **D** (0.5 mol%) is added to a solution of naphthol **1** or **4** (0.2 mmol) and pyrazolon-derived *N*-Boc ketimine **2** (0.22 mmol, 1.1 eq.) in CH_2Cl_2 (2 mL, 0.1 M). The reaction mixture is stirred until complete conversion of the naphthol substrate as indicated by TLC. The solvent is removed under reduced pressure and the crude product is directly purified by flash column chromatography (silica, *n*-pentane / diethyl ether) to afford the desired product as a solid.

Acknowledgements

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Keywords: pyrazolone • ketimine • aza-Friedel-Crafts • organocatalysis • asymmetric synthesis

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COMMUNICATION

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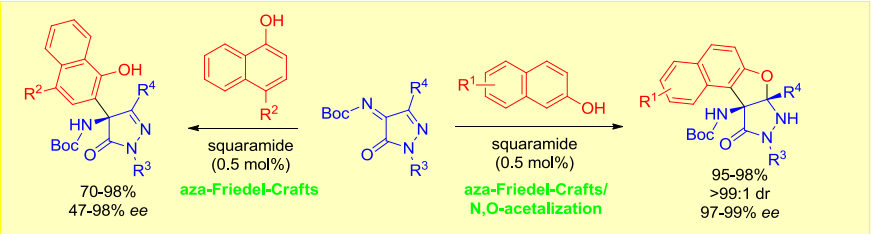
Page No. – Page No.

Asymmetric Squaramide Catalyzed Domino aza-Friedel-Crafts/N,O-Acetalization Reactions Between 2-Naphthols and Pyrazolinone Ketimines



A sub-mol% loading of a squaramide efficiently catalyzes a domino aza-Friedel-Crafts/N,O-acetalization reaction between 2-naphthols and *N*-Boc ketimines derived from pyrazolin-5-ones. The new protocol is scalable to gram amounts and leads to furanonaphthopyrazolidinones bearing two vicinal tetra-substituted stereocenters with excellent yields and stereoselectivities. With 1-naphthols and electron-rich phenols the corresponding amino-pyrazolone derivatives are formed.