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Brønsted acid catalyzed enantioselective addition of hydrazones to 3-indolylmethanols†

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The organocatalytic asymmetric addition of hydrazones to indole derivatives in the presence of chiral Brønsted acids is reported. A large variety of substrates are tolerated and the products are obtained in good yields and with excellent enantioselectivities. This metal-free reaction provides a convenient route to enantiopure β-substituted tryptophan derivatives in a concise fashion.

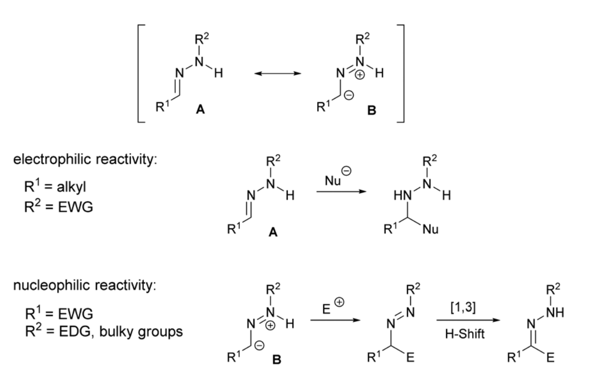
Introduction

In the last two decades, organocatalysis has attracted increasing interest from the chemical community.[1] The scientific endeavors in this research area led to a tremendous growth and organocatalysis has become a versatile tool to control the stereoselectivity and a complementary approach to metal catalysis.[2] However, emphasis has mainly been given to a narrow group of nucleophiles, including carbonyls, nitroalkanes, CH-acidic-, electron rich aromatic and heteroaromatic compounds due to their defined reactivity, easy synthesis and availability. Other versatile functional groups and molecules are often neglected. Hydrazones, for example, belong to the most versatile groups in terms of reactivity with only a few reported applications in asymmetric organocatalysis so far.[3] Depending on the substituents on the nitrogen and the azomethine carbon atom, hydrazones can either act as electrophile or nucleophilic acyl anion equivalents in Umpolung reactions (Scheme 1). There are also reports describing the nucleophilic addition of the nitrogen atom to electrophiles.[4] Thus, in order to control the ambident nucleophilicity of hydrazones and to avoid the formation of complex product mixtures, the substituents must be selected carefully. In this context, Fernández *et al.* reported the use of donor–acceptor-substituted hydrazones for the 1,4-addition to α,β-unsaturated aldehydes.[3f] In this protocol, the combination of an EWG on the azomethine carbon atom and a bulky EDG on the nitrogen atom enhances the nucleophilicity of the carbon atom as illustrated in structure **B**, thus preventing alkylation of the nitrogen (Scheme 1). In addition, the presence of electron withdrawing groups supports the Brønsted-acid-catalyzed [1,3]-hydride shift under mild conditions. The produced hydrazones, which can be considered as masked carbonyl equivalents, can then be further reacted.

Recently, the addition of nucleophiles to *in situ* generated indolyl iminium ions **D** has been reported (Scheme 2).[5] It was shown that 3-indolylmethanols **C** easily dehydrate in the presence of Brønsted acids to furnish stabilized iminium ions **D**.[6] In the case of chiral phosphoric acids, tight chiral contact ion pairs are formed, so that the subsequent vinylogous Mannich-type-reaction occurs in an asymmetric fashion.

Following a similar approach *via* a tight chiral contact ion pair intermediate, we anticipated that acceptor-donor substituted hydrazones would react with indolyl iminium ions to generate indolyl hydrazones which can be regarded as masked tryptophan derivatives.

Over the last few years, the replacement of amino acids in peptides with non-natural analogues has gained a major inter-



Scheme 1 General reactivity of hydrazones.

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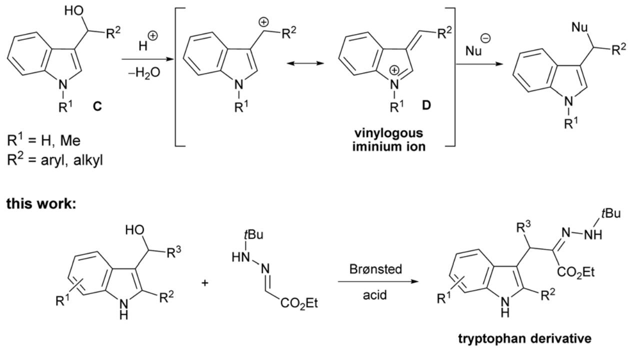


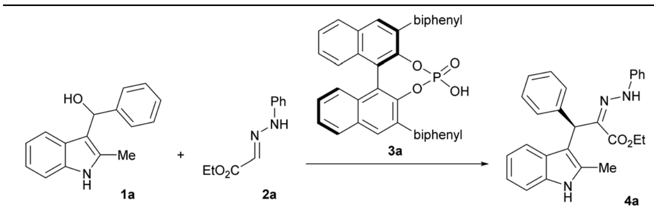
Scheme 2 Reactivity of 3-indolylmethanols.

est. Simple β-substituted analogues show great therapeutic impact in numerous biologically active peptides,[7] and they can be used to investigate peptide-receptor interactions.[8] However, the enantioselective synthesis of these analogues is still difficult to achieve. We herewith present a highly enantioselective method to access artificial tryptophan derivatives *via* a new asymmetric Brønsted acid catalyzed addition of hydrazones to 3-indolylmethanols.

Results and discussion

Initially we exploited the influence of different solvents for the synthesis of the targeted tryptophan derivatives. For this purpose, alcohol **1a** was reacted with hydrazone **2a** at 0 °C together with 5 mol% of Brønsted-acid **3a** (Table 1). To our delight full conversion of the starting material was achieved and the desired product **4a** was isolated in moderate yield and enantioselectivity. While chlorinated and polar solvents gave inferior or comparable results (entries 2–5), switching to

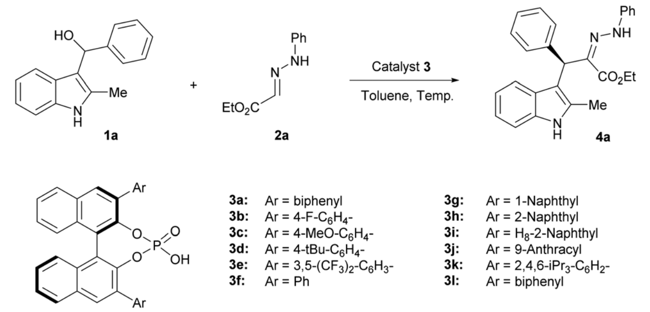
Table 1 Optimization of the reaction conditions – impact of solvent, temperature and reaction time on the reaction outcome



Entry[a]	Solvent	T (°C)	Time (d)	Yield[b] (%)	ee[c] (%)
1	$CHCl_3$	0	3	44	32
2	DCM	0	3	15	22
3	DCE	0	3	34	21
4[d]	THF	rt	3	49	37
5[d]	CH_3CN	rt	5	20	17
6	Toluene	0	3	78	57
7	Ph-CF_3	0	3	39	36
8[d]	Benzene	rt	2	68	34
9	*o*-Xylene	0	1	54	56
10	Mesitylene	0	1	63	58
11[d]	*n*-Hexane	rt	5	—	—

[a] Reaction conditions: **1a** (0.13 mmol), **2a** (0.10 mmol), **3a** (5 mol%), solvent (2 ml). [b] Yield of isolated **4a** after full conversion of the starting material. [c] Determined by HPLC or SFC on chiral stationary phases. [d] Reactions were conducted at rt as no significant product formation was observed at 0 °C.

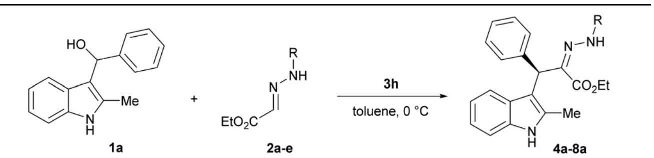
Table 2 Screening of different catalysts and reaction conditions



Entry[a]	Catalyst	T (°C)	Time (d)	Yield[b] (%)	ee[c] (%)
1	**3a**	0	3	78	57
2	**3b**	0	2	59	46
3	**3c**	0	2	40	44
4	**3d**	0	2	26	51
5	**3e**	0	2	32	19
6	**3f**	0	2	44	41
7	**3g**	0	7	39	36
8	**3h**	0	2	68	65
9	**3i**	0	2	68	65
10	**3j**	0	7	15	19
11	**3k**	0	7	10	34
12[d]	**3l**	0	3	15	44
13	**3f**	−25	7	40	63
14	**3f**	−40	7	50	70
15	**3h**	−20	2	78	68
16[e]	**3h**	0	2	73	64

[a] Reaction conditions: **1a** (0.13 mmol), **2a** (0.10 mmol), **3** (5 mol%), toluene (2 ml). [b] Yield of isolated **4a** after full conversion of the starting material. [c] Determined by HPLC or SFC on chiral stationary phases. [d] Triflamide catalyst **3l** with NHTf instead of OH. [e] Reaction with addition of 4 Å molecular sieves.

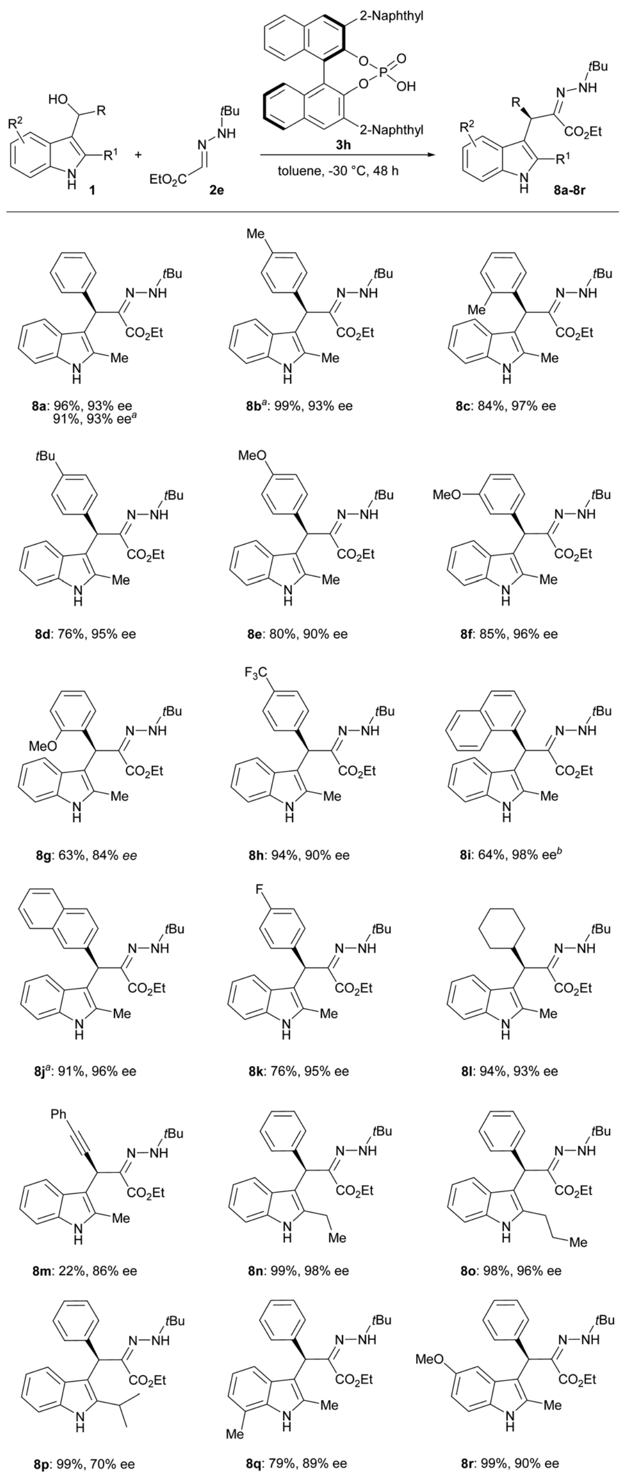
Table 3 Evaluation of different hydrazones



Entry[a,b]	2	R	Time (d)	Yield[c] (%)	ee[d] (%)
1	**2a**	Ph	2	68	65
2	**2b**	4-MeO-Ph	1	82	70
3	**2c**	4-Cl-Ph	2	20	60
4	**2d**	Me	1	41	29
5	**2e**	*t*Bu	1	41	77
6[e]	**2e**	*t*Bu	2	96	93

[a] Reaction conditions: **1a** (0.13 mmol), **2** (0.10 mmol), **3h** (5 mol%), toluene (2 ml), 0 °C. [b] **4a:** R = Ph; **5a:** R = 4-MeO-Ph; **6a:** R = 4-Cl-Ph; **7a:** R = Me; **8a:** R = *t*Bu. [c] Yield of isolated **4a–8a** after full conversion of the starting material. [d] Determined by HPLC or SFC on chiral stationary phases. [e] Reaction at −30 °C.

unpolar benzene derivatives seemed more promising (entries 6–10). In the case of toluene, **4a** was isolated with 78% yield and 57% ee.



Scheme 3 Substrate scope of the organocatalytic enantioselective addition of hydrazones to 3-indolylmethanols. Reaction conditions: 0.13 mmol **1**, 0.10 mmol **2e**, 5 mol% **3h**, 2 ml toluene, −30 °C, 48 h. The enantiomeric excess was determined by HPLC or SFC on chiral stationary phases. [a]1 mmol **1**. [b]72 h.

Thus, toluene was selected for further optimization studies. Interestingly, no conversion occurred in hexane due to the insufficient solubility of the reactants and catalyst (entry 11).

After solvent optimization, we turned our attention to different Brønsted-acid catalysts (Table 2). It turned out, that the steric bulk introduced at the backbone of the BINOL moiety has a major impact on the reactivity and selectivity. In this context, only Brønsted-acids **3h** and **3i** performed better than **3a** in terms of yields and enantioselectivity. As catalyst **3i** led to the same results as **3h**, we decided to use **3h** due to its easier synthesis. Interestingly, unlike anticipated, the more acidic triflamide catalyst **3l** gave inferior results (entry 12). Once the optimal catalyst was found, we investigated the effect of temperature on the reaction outcome. We found that by decreasing the temperature, improved enantioselectivities were obtained. At −20 °C product **4a** was isolated with 78% yield and 68% ee (entry 15). In addition, the presence of 4 Å molecular sieves did not have any beneficial effect on the outcome of the reaction (entry 16).

Having established the best conditions with respect to solvent, catalyst and temperature, we tried to apply different hydrazones to further improve the enantiomeric excess (Table 3). The electron donating methoxy group (entry 2) led to an improved yield and ee-value, whereas the presence of an electron withdrawing group (entry 3) led to the opposite result, as expected. Even better results were achieved by applying hydrazones with a *tert*-butyl substituent (entry 5). By lowering the reaction temperature to −30 °C product **8a** was isolated with excellent yield (96%) and a very good enantiomeric excess (93% ee).

With the optimal reaction conditions in hand, we assessed the substrate scope of the hydrazone addition (Scheme 3). We achieved very good results with substrates bearing EDG (**8b–g**) with yields up to 99% and enantioselectivity values up to 97%. Furthermore, the products were formed with good yields and enatioselectivites with EWG groups as trifluoromethyl (**8h**) and fluorine (**8k**) at the phenyl ring, as well as for bulky groups (**8i–j**). The protocol works also well for non-aromatic substituents with 94% yield and 93% ee for a cyclohexyl substituent (**8k**) and also with an acetylene substituent (**8m**) whereas the yield dropped to 22% in this case.

In addition, it is also possible to synthesize backbone-substituted tryptophan derivatives in a high enantiomeric purity. Different substituents at the indole 2-position as well as substituents in the 5- and 7-position were tolerated, and the products **8n–r** were obtained with good yields and with excellent enantiomeric excess (up to 98%). The absolute configuration of product **8i** was determined as *R* by CD spectroscopy.

Conclusions

In conclusion we have developed a general metal-free highly enantioselective method which allows the synthesis of artificial tryptophan derivatives. The chiral phosphoric acid **3h** enables the addition of donor-substituted hydrazones to

3-indolylmethanols in excellent yields and with excellent enantioselectivity values.

Author contributions

M.R., S.M., and M.S.M. conceived and designed the project. S.M., M.S.M. and I.A. performed the experiments and analysis.

Conflicts of interest

There are no conflicts to declare.

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