Asymmetric Synthesis

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Asymmetric Brønsted Acid Catalyzed Synthesis of Triarylmethanes—Construction of Communesin and Spiroindoline Scaffolds

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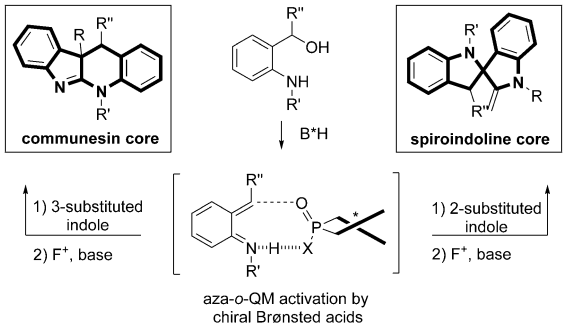
Abstract: *Aza-ortho-quinone methides allow the straightforward asymmetric synthesis of natural-product-inspired indole scaffolds possessing a quaternary stereocenter. Our approach provides access to diverse communesin and spiroindoline derivatives with high enantioselectivity under mild reaction conditions. Predictable substitution patterns are found to be the key to our regiodivergent protocols.*

The development of shorter synthetic routes for assembling complex molecules with potential drug character is of great interest from a synthetic as well as both ecological and economical points of view. Therefore, the development of efficient atom- and step-economical synthetic pathways is one of the main goals in chemical synthesis.[1] The communesin[2] and spiroindoline[3] skeletons are core structural elements in a wide range of natural and synthetic products. Alkaloids possessing these indole-derived heterocycle frameworks exhibit a broad spectrum of biological activities and potential for pharmacological drug discovery. However, progress in the development of these important targets, especially in enantioselective form, is relatively slow,[4,5] particularly due to the complexity of the precursor structures and the difficulty in finding a suitable chiral catalyst. Therefore we decided to develop a catalytic asymmetric reaction protocol to build triarylmethanes[6] which serve as precursors for the synthesis of desired communesin and spiroindoline structures (Scheme 1). Complete control in the synthesis of these structurally different products can be achieved through the installation of a suitable substituent at specific positions in the indole starting material. Furthermore, the key to the success of this asymmetric strategy relies on the judicious choice of the aza-*ortho*-quinone methide (aza-*o*-QM)[7] intermediate and the chiral catalyst.

Aza-*o*-QMs[7] are reactive intermediates in the biosynthesis of natural products. Their high reactivity, which is due to the driving force of rearomatization, can also be employed in organic synthesis. Therefore, harnessing this unique characteristic provided a new entry toward the synthesis of complex natural product frameworks as well as unnatural molecules for drug design.[2d,e] Recent research has started to focus on asymmetric catalytic variants as well, due to the increasing number of chiral drugs identified in which enantiomers proved to have significantly different effects in vivo.[8] Considerable efforts have been devoted to the generation of aza-*o*-QMs over the last decades,[9] including thermal extrusions, photolysis and acid- or base-mediated transformations. Yet, aza-*o*-QMs have been less thoroughly studied in catalytic asymmetric synthesis,[10,11] potentially due to the difficulties associated with the stabilization of these highly reactive species.



Scheme 1. Aza-*o*-QMs as crucial intermediates in the enantioselective synthesis of natural-product-inspired scaffolds.

In this context the challenge consists in the rational choice of a suitable chiral catalyst which can strike a right balance between reactivity and stability. Here we report an efficient regiodivergent Brønsted acid catalyzed protocol for the rapid synthesis of diverse communesin and spiroindoline structures with quaternary carbon stereocenters. The formation of highly reactive aza-o-QM species is the key to success.

Brønsted acids, especially chiral phosphoric acids, have proved to be highly efficient catalysts for a wide range of asymmetric transformations under mild reaction conditions.[12] The combination of Brønsted acid catalysis and reactions of aza-*o*-QMs is promising for the development of asymmetric transformations involving such reactive intermediates. Classically, chiral phosphoric acids and derivatives serve as bifunctional catalysts to lower the LUMO of electrophiles by H-bonding and they activate the acidic nucleophiles via the phosphoryl oxygen. Indeed, these catalysts should also have the potential to strongly coordinate to aza-*o*-QMs providing activation of the imine group by hydrogen bonding or ion pairing,[13] and controlling the selectivity of the addition with the attacking nucleophiles.

With these considerations in mind, we began our investigation on the functionalization of 2-substituted indoles.

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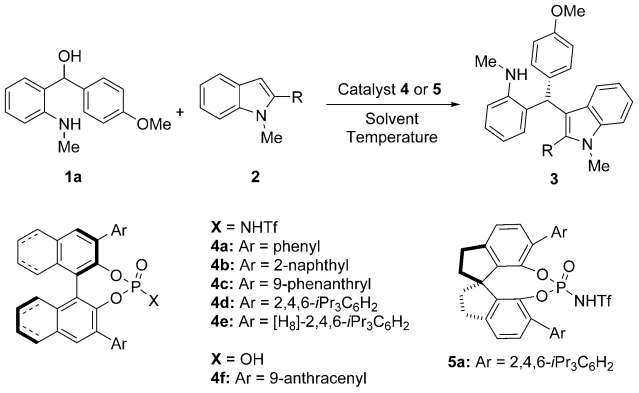
Ortho-amino benzyl alcohol **1a** was chosen as the starting point for the in situ generation of aza-*o*-QM by means of acid. Initial experiments were conducted in the presence of 5 mol% of *N*-triflylphosphoramides (NTPAs) **4a–e** (Table 1). With 3,3′-biphenyl-substituted *N*-triflylphosphoramide **4a** the reaction between alcohol **1a** and indole **2a** led to the formation of **3a** in nearly racemic form (entry 1).

Table 1: Optimization of the Brønsted acid catalyzed reaction between in situ generated aza-*o*-QM and 2-substituted indoles.



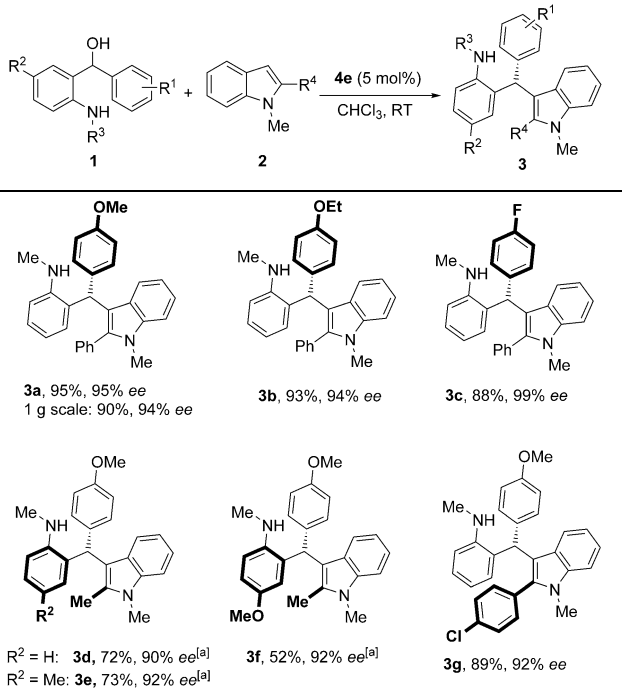
Entry[a]	Solv.	R	Temp.	4/5	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	Me	0°C	**4a**	56	6
2	CH_2Cl_2	Me	0°C	**4b**	65	4
3	CH_2Cl_2	Me	0°C	**4c**	71	17
4	CH_2Cl_2	Me	RT	**4d**	84	74
5	CH_2Cl_2	Me	RT	**4e**	98	80
6	CH_2Cl_2	Me	RT	**5a**	94	25[d]
7	toluene	Me	RT	**4e**	83	73
8	$CHCl_3$	Me	RT	**4e**	98	87
9	DCE	Me	RT	**4e**	97	87
10	$CHCl_3$	Me	10°C	**4e**	72	90
11	$CHCl_3$	Me	0°C	**4e**	57	90
12	$CHCl_3$	H	RT	**4e**	98	35
13	$CHCl_3$	Ph	RT	**4e**	95	95

[a] Reactions were performed with alcohol **1a** (0.05 M), indole **2** (1.1 equiv), and 5 mol% catalyst. The solution was stirred for 3 days until **1a** was completely consumed. [b] Yield of isolated products after column chromatography. [c] Enantiomeric excess was determined by HPLC on a chiral stationary phase. [d] Opposite enantiomer.

We anticipated that the steric nature of NTPA plays a critical role for the enantioselectivity and evaluated bulkier catalysts. The sterically congested 3,3′-bis(2,4,6-*i*Pr$_3$C$_6$H$_2$)-substituted [H$_8$]-NTPA **4e** afforded the optimal combination in terms of reactivity and selectivity (entry 5). Switching to the spirocyclic catalyst **5a** did not provide a satisfactory result in terms of selectivity (entry 6). Different aromatic and chlorinated solvents were evaluated (entries 7–9) and we obtained the best results in terms of reactivity and selectivity for the reaction in chloroform (entry 8). Subsequent evaluation of the reaction temperature (entries 10 and 11) revealed 10°C to be optimal (entry 10). With the best reaction conditions in hand, we assessed the influence of the substituent at the C2-position of indole on the reaction outcome (entries 12 and 13). Gratifyingly the best yield and enantioselectivity were achieved when a phenyl group was present at C2 (95%, 95% *ee*; entry 13).

With the optimal reaction conditions identified, we explored the scope of the Brønsted acid catalyzed Michael addition of indoles and aza-*o*-QMs (Table 2). Gratifyingly, we found that the core structure of aza-*o*-QM could be readily decorated at different positions and the reactions proceeded smoothly for a broad range of substrates. In general, diverse substrates with different substitution patterns and electronic properties provided the desired products **3** with good reactivity and excellent selectivity (Table 2).

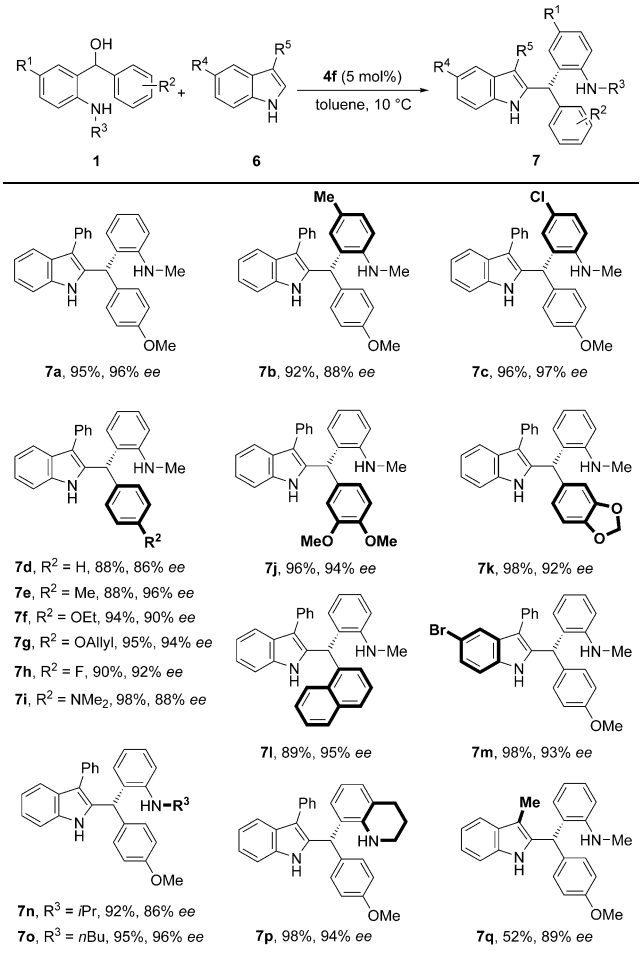
Table 2: Substrate scope of the Brønsted acid catalyzed reaction.



Conditions: Reactions were performed with alcohol **1** (0.05 M), indole **2** (1.1 equiv), and 5 mol% **4e**. The solution was stirred for 3 days at room temperature. Yield of isolated products after column chromatography. The enantiomeric excess was determined by HPLC on a chiral stationary phase. [a] Reaction was performed at 10°C.

We next put our efforts into the synthesis of C2-functionalized indoles.[14] We hypothesized that blocking the C3 position on indole should switch the functionalization process in favor of the C2 position. Table 3 shows the generality of this regioselective reaction. The steric and electronic nature of the substituents had little influence on the reaction outcome and all substrates delivered products with very high yields and selectivities. Initially, substrates bearing substituents R^1 with different electronic properties were used and the corresponding adducts **7a–c** were isolated with excellent yields (92–96%) and enantioselectivities (88–96% *ee*). We then explored the influence of the electronic properties of the substituent R^2. Substrates with electron-donating or -withdrawing substituents as well as with R^2 = H were tested and all participated smoothly in this process, furnishing the corresponding products **7d–i** with very good

Table 3: Substrate scope of the Brønsted acid catalyzed C2-functionalization of 3-substituted indoles with aza-*o*-QMs.[a]



[a] Conditions: Reactions were performed with alcohol **1** (0.05 M), indole **6** (1.1 equiv), and 5 mol% **4f**. The solution was stirred for 3 days at room temperature. Yield of isolated products **7a**–**p** after column chromatography. The enantiomeric excess was determined by HPLC on a chiral stationary phase.

results (88–98%, 86–96% *ee*). Sterically more demanding substrates were also amenable and provided good results. 6-Bromoindole was submitted also to the reaction conditions and afforded the product **7m** with 98% yield and 93% *ee*. This versatile product shows the potential for further diversification via conventional metal-catalyzed cross-coupling reactions. Furthermore, the use of sterically more demanding amines did not affect the reaction outcome (**7n**–**p**: 92–98%, 86–96% *ee*). 3-Methylindole could also be used and the corresponding product **7q** was isolated in 52% yield and 89% *ee*. The absolute configuration of product **7c** was determined by X-ray single-crystal structure analysis.[15]

Based on our observations we propose a plausible mechanism for this Brønsted acid catalyzed regioselective addition process, which is depicted in Figure 1. The formation of complex **A** provides a rigid stereochemical environment for the subsequent Michael addition with carbon–carbon bond formation through the less sterically impeded trajectory, thus affording the *S*-configured stereocenter in the process.

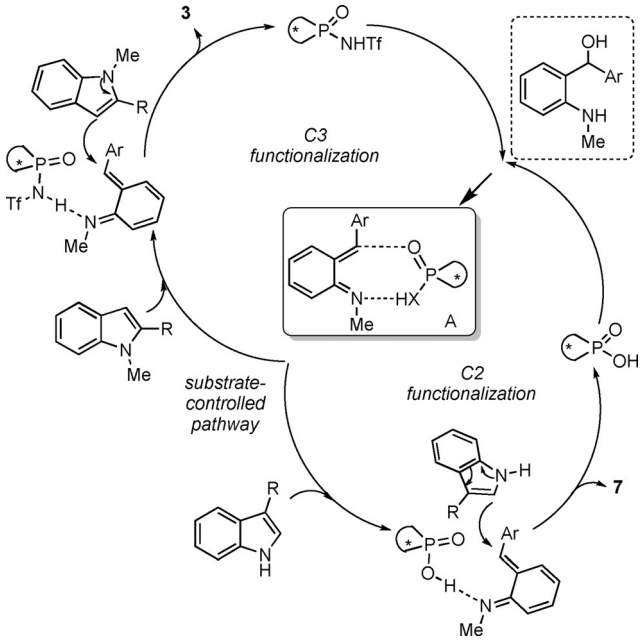
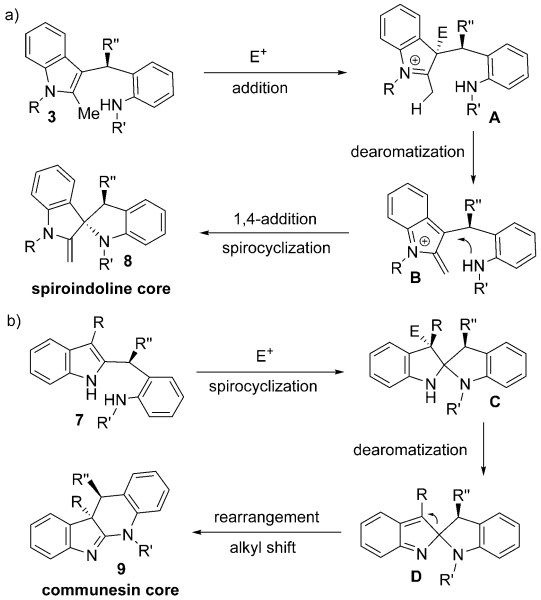


Figure 1. Proposed mechanism for the Brønsted acid catalyzed addition of indoles to aza-*o*-QMs.

Particularly noteworthy is that interception of intermediate **A** by differently substituted indoles results in a controllable switch in regioselectivity.

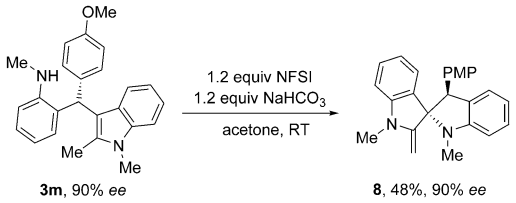
Based on a retrosynthetic analysis, we decided to develop new methods for converting the regiodivergent products from the Brønsted acid catalysis into more complex structures with communesin (**9**) or spiroindoline (**8**) cores (Scheme 2).

In principle, the reaction of **3** with an electrophile results in intermediate **A** which gives the Michael acceptor **B** after deprotonation and dearomatization. The subsequent 1,4-addition would lead to the desired spiroindoline skeleton



Scheme 2. Proposed mechanism for the cyclization of triarylmethanes.

(Scheme 2a). On the other hand, the reaction of **7** with an electrophile should enable a subsequent spirocyclization which results in **C**. Subsequent deprotonation would result in a rearrangement in terms of a 1,4-addition, to provide the desired communesin framework (Scheme 2b). Neither reaction sequence has been described previously and both should lead to an easy and quick access to enantiomerically enriched products. Therefore, we decided to attempt these new synthetic pathways for the synthesis of natural-product-inspired indole derivatives with quaternary stereocenters. After a number of attempts we accomplished the synthesis of spiroindoline **8** by means of a NFSI-mediated addition/deprotonation/deprotonation/spirocyclization sequence starting from **3m** (Scheme 3).

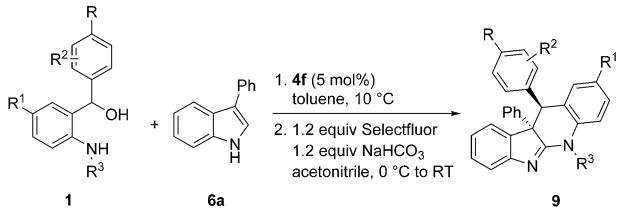


3m, 90% *ee* **8**, 48%, 90% *ee*

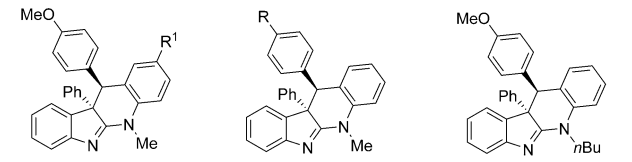
Scheme 3. Asymmetric synthesis of the natural-product-inspired molecular framework **8**.

Furthermore, the synthesis of communesin framework **9** with quaternary stereocenters was realized in a one-pot reaction for a variety of substrates. The asymmetric Brønsted acid catalyzed reaction of **1** with indole **6a** led to **7**. Selectfluor[16] triggered a fluorination/cyclization/rearrangement sequence, which allowed a short and efficient synthetic route to the optically active alkaloids **9a–h** (Table 4).[17]

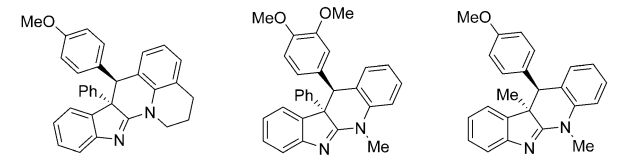
Table 4: Substrate scope of the Brønsted acid catalyzed one-pot reaction for the synthesis of communesin core **9**.



1 **6a** **9**



9a, R^1 = H, 89%, 98% *ee*
9b, R^1 = Cl, 92%, 95% *ee*
9c, R = OAllyl, 90%, 95% *ee*
9d, R = Me, 86%, 92% *ee*
9e, 94%, 95% *ee*



9f, 73%, 92% *ee* **9g**, 83%, 95% *ee* **9h**, 31%, 91% *ee*

In summary, we have developed a substrate-controlled strategy for the enantioselective synthesis of skeletally diverse communesin and spiroindoline scaffolds. Our results clearly indicate that both the aza-*o*-QM intermediates produced in situ as well as the chiral phosphoric acid or phosphoramide catalysts play major roles in these efficient transformations. Moreover, the readily available substrates, the operational simplicity, and the complexity of the resulting natural-product-inspired frameworks are particularly impressive. In addition to the new regiodivergent, asymmetric Brønsted acid catalyzed addition of indoles to aza-*ortho*-quinones, we also describe a new addition/spirocyclization sequence that leads, depending on the indole derivative, to communesin and spiroindoline cores with quaternary stereocenters. Further studies regarding the detailed mechanism and application of this newly developed methodology toward the synthesis of natural products[18] are currently being pursued in our laboratories and will be reported in due course.

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Keywords: counterions · fluorine · Michael addition · organocatalysis · rearrangements

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