Dearomatization

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Organocatalytic Asymmetric Arylative Dearomatization of 2,3-Disubstituted Indoles Enabled by Tandem Reactions**

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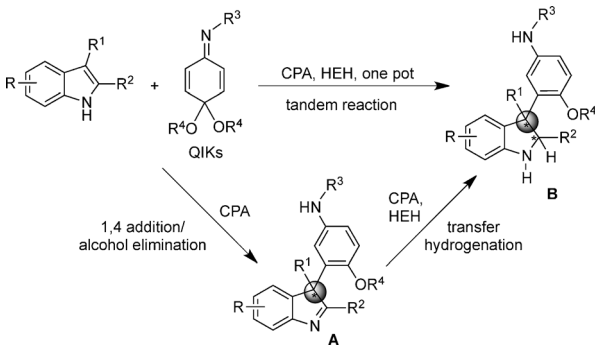
Abstract: *The organocatalytic asymmetric arylative dearomatization of indoles was achieved through two tandem approaches involving 2,3-disubstituted indoles and quinone imine ketals. One approach utilized the enantioselective cascade 1,4 addition/alcohol elimination reaction, the other employed the one-pot tandem arylative dearomatization/transfer hydrogenation sequence. In both cases, enantiomerically pure indole derivatives that bear an all-carbon quaternary stereogenic center were generated in high yields and excellent stereoselectivities (all d.r. > 95:5, up to 99 % ee).*

Dearomatization of aromatic or heteroaromatic compounds is a robust method for the preparation of cyclic or heterocyclic frameworks that constitute the core structures of numerous natural products and pharmaceuticals.[1] In particular, catalytic asymmetric dearomatization (CADA) reactions have shown great potential for the conversion of simple planar aromatic molecules into enantioenriched ring systems with structural complexity.[2] Therefore, a great deal of attention has been paid to CADA reactions and elegant methods have been developed in oxidative dearomatization, alkylative dearomatization and so on.[2] In sharp contrast, the catalytic asymmetric arylative dearomatization has been scarcely investigated[3] despite its great importance in organic synthesis.[4] More surprisingly, even racemic arylative dearomatizations are rather limited.[5] Recently, the groups of Buchwald,[3a] You,[3b] and MacMillan[3c] independently established methods for the metal-catalyzed asymmetric arylative dearomatization of phenols or indoles. Despite their creative work, this type of reaction is still relatively underdeveloped. Moreover, because of the importance of indole derivatives,[6] the development of multiple strategies for the arylative dearomatization of indole derivatives is highly desirable.

Given the inherent advantages of organocatalytic asymmetric tandem reactions,[7] we decided to apply this strategy to the enantioselective arylative dearomatization of indole derivatives. In this context, quinone imine ketals (QIKs)[8] were selected as aryl group surrogates to accomplish this task. However, QIKs are rarely employed in catalytic asymmetric transformations[8h] and contain multiple electrophilic sites. This latter issue makes controlling the regio- and enantioselectivity of QIK-involved reactions a formidable challenge.

Inspired by these challenges and our previous work with asymmetric organocatalysis,[9] we designed an organocatalytic asymmetric tandem reaction of 2,3-disubstituted indoles and QIKs to accomplish the arylative dearomatization of indoles in a regio-, diastereo-, and enantioselective manner (Scheme 1). In the presence of chiral phosphoric acid (CPA) as a privileged organocatalyst,[10] the two substrates were simultaneously activated by H-bond interactions to initiate an enantioselective 1,4 addition/alcohol elimination cascade. This led to the generation of the arylative dearomatization product **A**, which underwent further stereoselective transfer hydrogenation with a Hantzsch ester (HEH),[11] again promoted by CPA, to produce a second arylative dearomatization product **B**. Importantly, product **B** was directly obtained by the tandem arylative dearomatization/transfer hydrogenation sequence in a one-pot fashion.



Scheme 1. Organocatalytic asymmetric tandem reactions that lead to the arylative dearomatization of indole derivatives.

Initially, we employed the cascade reaction of 2,3-dimethylindole **1a** with QIK **2a** in the presence of a CPA (**4** or **5a**) to confirm our hypothesis. The substrates smoothly underwent the arylative dearomatization to afford product **3aa** with a quaternary stereogenic center (Scheme 2, see the Supporting Information for details on the optimization of reaction conditions).

With the optimal conditions known, we then investigated the substrate scope of the cascade arylative dearomatization reaction (Table 1). This protocol was applicable to a wide range of 2,3-disubstituted indoles **1** bearing different $R^1/R^2/R^3$ groups (Table 1, entries 1–13), delivering the target product **3** in generally high yields and excellent enantioselectivities (up to 99 % yield, 99 % *ee*). In general, 2,3-disubstituted indoles

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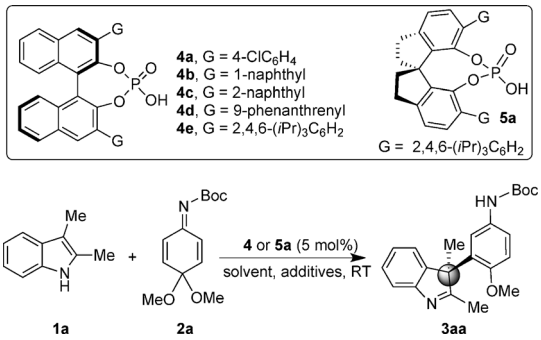
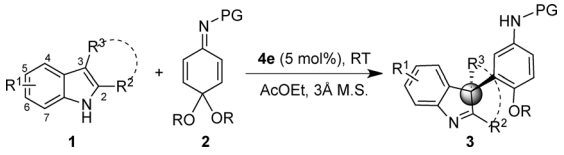


Scheme 2. Catalysts and model reaction used to optimize the reaction conditions.

Table 1: Substrate scope of the cascade arylative dearomatization reaction.[a]



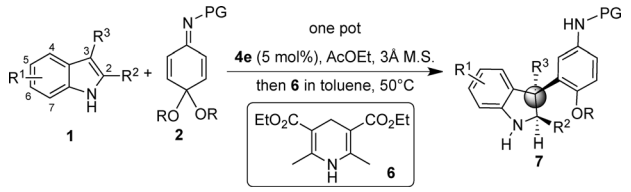
Entry	$R^1/R^2/R^3$ (**1**)	R/PG (**2**)	**3**	Yield [%][b]	*ee* [%][c]
1	H/Me/Me (**1a**)	Me/Boc (**2a**)	**3aa**	92	94
2	4-Me/Me/Me (**1b**)	Me/Boc (**2a**)	**3ba**	82	96
3	4-Cl/Me/Me (**1c**)	Me/Boc (**2a**)	**3ca**	94	89
4	5-Me/Me/Me (**1d**)	Me/Boc (**2a**)	**3da**	99	95
5	5-F/Me/Me (**1e**)	Me/Boc (**2a**)	**3ea**	93	93
6	5-Cl/Me/Me (**1f**)	Me/Boc (**2a**)	**3fa**	66	90
7	5-Br/Me/Me (**1g**)	Me/Boc (**2a**)	**3ga**	78	96
8	6,7-Me_2/Me/Me (**1h**)	Me/Boc (**2a**)	**3ha**	75	91
9	7-Me/Me/Me (**1i**)	Me/Boc (**2a**)	**3ia**	83	88
10[d]	7-F/Me/Me (**1j**)	Me/Boc (**2a**)	**3ja**	54	99
11	H/Et/Me (**1k**)	Me/Boc (**2a**)	**3ka**	77	94
12	H/Me/Et (**1l**)	Me/Boc (**2a**)	**3la**	65	95
13[d]	H/-$(CH_2)_4$- (**1m**)[e]	Me/Boc (**2a**)	**3ma**	58	95
14	H/Me/Me (**1a**)	Et/Boc (**2b**)	**3ab**	72	97
15	H/Me/Me (**1a**)	*i*Pr/Boc (**2c**)	**3ac**	67	99
16	H/Me/Me (**1a**)	*n*Bu/Boc (**2d**)	**3ad**	81	94
17	H/Me/Me (**1a**)	Me/Cbz (**2e**)	**3ae**	87	94
18	H/Me/Me (**1a**)	Me/Bz (**2f**)	**3af**	99	89
19[d]	H/Me/Me (**1a**)	Me/Ac (**2g**)	**3ag**	84	82

[a] Unless otherwise indicated, the reaction was carried out at a 0.1 mmol scale and catalyzed by 5 mol% **4e** in AcOEt (0.5 mL) with 3 Å M.S. (50 mg) at RT for 12 h. The molar ratio of **1**:**2** was 3:1. [b] Yields of isolated products. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] 20 mol% **4e** was used. [e] **1m** = tetrahydrocarbazole. M.S. = molecular sieves.

with a variety of substituents at different positions (C4–C7) of the phenyl moiety could be successfully utilized in the reaction (Table 1, entries 1–10). Moreover, the alkyl groups at positions C2 and C3 could be elongated with retained enantioselectivities (Table 1, entries 11 and 12). Notably, the cyclic tetrahydrocarbazole **1m** participated smoothly in the desired reaction, affording the polycyclic product **3ma** with a high enantioselectivity (Table 1, entry 13). The substrate scope of QIKs **2** was also evaluated by their reaction with 2,3-dimethylindole (**1a**; Table 1, entries 14–19). The alkoxy groups of the QIKs could be altered from a methoxy group to linear or branched chains (Table 1, entries 1 and 14–16). Branched alkoxy groups, such as *iso*-propoxy, resulted in a better enantioselectivity but were less reactive (Table 1, entry 15 versus 1, 14, and 16). Besides, the use of the N-protecting groups Boc and Cbz resulted in higher enantioselectivities than the use of Bz and Ac functionalities (Table 1, entries 1 and 17 versus 18 and 19).

Subsequently, the above-described reaction was combined with a transfer hydrogenation in a tandem reaction sequence. This one-pot strategy afforded a second series of arylative dearomatization products from easily available starting materials. To obtain the best results, the reaction conditions were again optimized accordingly (see the Supporting Information for details). This second tandem reaction was amenable to a variety of 2,3-disubstituted indoles **1** (Table 2,

Table 2: Substrate scope of the one-pot tandem arylative dearomatization/transfer hydrogenation sequence.[a]



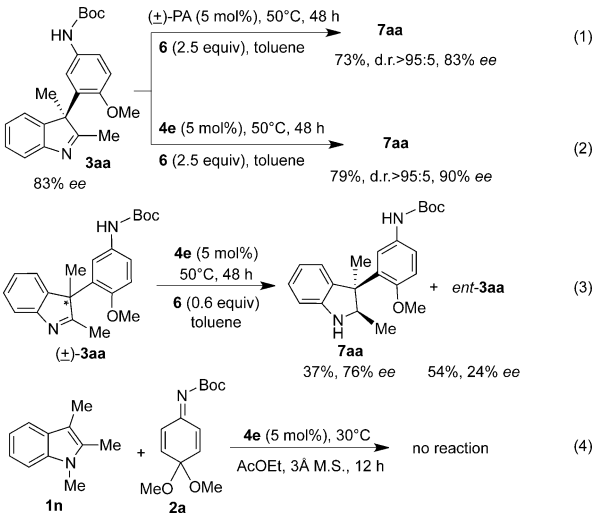
Entry	$R^1/R^2/R^3$ (**1**)	R/PG (**2**)	**7**	Yield [%][b]	*ee* [%][c]
1	H/Me/Me (**1a**)	Me/Boc (**2a**)	**7aa**	82	99
2	4-Me/Me/Me (**1b**)	Me/Boc (**2a**)	**7ba**	71	>99
3	5-Me/Me/Me (**1d**)	Me/Boc (**2a**)	**7da**	60	99
4	5-F/Me/Me (**1e**)	Me/Boc (**2a**)	**7ea**	70	97
5	5-Cl/Me/Me (**1f**)	Me/Boc (**2a**)	**7fa**	63	96
6	5-Br/Me/Me (**1g**)	Me/Boc (**2a**)	**7ga**	77	95
7	6,7-Me_2/Me/Me (**1h**)	Me/Boc (**2a**)	**7ha**	61	99
8	7-Me/Me/Me (**1i**)	Me/Boc (**2a**)	**7ia**	69	97
9	7-F/Me/Me (**1j**)	Me/Boc (**2a**)	**7ja**	61	98
10[d]	H/Et/Me (**1k**)	Me/Boc (**2a**)	**7ka**	41	96
11	H/Me/Et (**1l**)	Me/Boc (**2a**)	**7la**	61	>99
12	H/Me/Me (**1a**)	Et/Boc (**2b**)	**7ab**	68	99
13	H/Me/Me (**1a**)	*i*Pr/Boc (**2c**)	**7ac**	51	97
14	H/Me/Me (**1a**)	*n*Bu/Boc (**2d**)	**7ad**	81	99
15	H/Me/Me (**1a**)	Me/Cbz (**2e**)	**7ae**	52	99

[a] Unless otherwise indicated, the reaction was carried out at a 0.1 mmol scale and catalyzed by 5 mol% **4e** in AcOEt (0.5 mL) with 3 Å M.S. (50 mg) at RT for 12 h. HEH (**6**) in toluene (1 mL) was then added to the reaction mixture, which was stirred at 50°C for 48 h. The molar ratio of **1**:**2**:**6** was 3:1:2.5. All d.r. > 95:5, determined by ^{1}H NMR spectroscopy. [b] Yields of isolated products. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] Performed by a stepwise procedure for 72 h.

entries 1–11) and QIKs **2** (entries 12–15) in the presence of catalyst **4e** and HEH (**6**). Products **7** were obtained with two adjacent stereogenic centers, including one all-carbon quaternary stereogenic center, with perfect diastereoselectivities (all d.r. > 95:5) and enantioselectivities (95–99% *ee*). Reactions with 2,3-disubstituted indoles bearing electronically rich, neutral, and poor substituents at C4–C7 (Table 2, entries 1–9), or with various alkyl groups at C2–C3 (Table 2, entries 10

and 11), resulted in high degrees of stereoselectivity, albeit with different yields. As above, QIKs that bear branched alkoxy groups were less reactive than those bearing linear alkoxy groups (Table 2, entries 13 versus 12 and 14).

Notably, the *ee* values of products **7** from tandem arylative dearomatization/transfer hydrogenation reactions were generally higher than those of products **3** produced by the 1,4 addition/alcohol elimination cascade (Table 2 versus Table 1). Several control experiments were performed to gain insight into this phenomenon (Scheme 3). Initially, compound **3aa** (83% *ee*) was subjected to a transfer hydrogenation in the

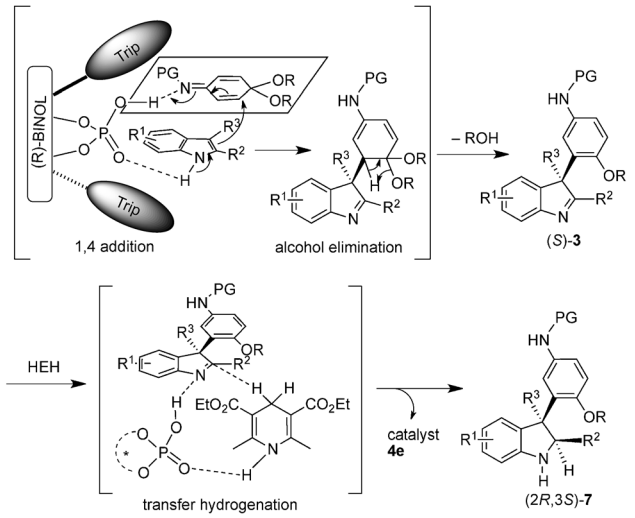


Scheme 3. Control experiments to investigate the reaction pathway.

presence of racemic phosphoric acid ((±)-PA) and CPA **4e** [Eq. (1) and (2), respectively]. In both cases, product **7aa** was obtained in similar yields and excellent diastereoselectivities. However, (±)-PA afforded the product in a maintained enantioselectivity of 83% *ee* [Eq. (1)], while CPA **4e** resulted in an enhanced enantioselectivity of 90% *ee* [Eq. (2)]. The d.r. > 95:5 of **7aa** indicated that the original chiral center of **3aa** imposed a strong inductive effect on the formation of a second chiral center in **7aa**. Besides, the elevated *ee* value of 90% from the transformation catalyzed by CPA **4e** implied that there might be a kinetic resolution of **3aa** during the transfer hydrogenation process. To confirm this hypothesis, racemic **3aa** was reacted with 0.6 equiv of HEH (**6**) under standard conditions catalyzed by CPA **4e** [Eq. (3)]. The reaction afforded **7aa** in 76% *ee* and the recovered *ent*-**3aa** in 24% *ee*, thus verifying that a moderate degree of kinetic resolution of **3aa** exists in the asymmetric transfer hydrogenation process catalyzed by CPA **4e**.

The role of the NH group in substrate **1** was also investigated by reacting the N-protected substrate **1n** with QIK **2a** under the optimized conditions [Eq. (4)]. No reaction was observed, thus implying that the NH group of the 2,3-disubstituted indole plays a crucial role in the reaction through the formation of a H-bond with the catalyst.[12]

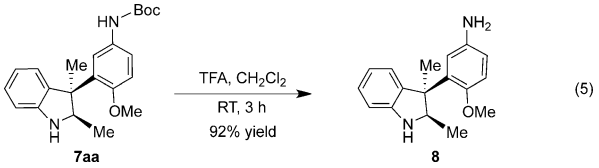
The absolute configuration of compounds **3ea** and **7aa** (all *ee* > 99% after recrystallization) were unambiguously determined to be (*S*) and (2*R*,3*S*), respectively, by single-crystal X-ray diffraction analyses (see the Supporting Information for details).[13] The absolute configurations of products **3** and **7** were assigned by analogy. Based on the experimental results, a possible reaction pathway that explains the stereochemistry of the reaction is illustrated in Scheme 4. CPA **4e** acts as a bifunctional catalyst to simultaneously activate 2,3-disubstituted indoles and QIKs through dual H-bond activation, which promotes the first step of the enantioselective 1,4



Scheme 4. Proposed reaction pathway.

addition/alcohol elimination cascade. The arylative dearomatization products **3** are thus obtained with (*S*) configuration because of the chiral environment generated by the (*R*)-BINOL backbone and 3,3′-TRIP groups of CPA **4e**. Then, in the presence of HEH and CPA **4e**, the second step of the transfer hydrogenation occurs with enhanced stereoselectivity as a result of the inductive effect of the first chiral center as well as the kinetic resolution facilitated by catalyst **4e**, to afford the experimentally observed (2*R*,3*S*)-configured product **7**.

The N-Boc protecting group in **7aa** can be removed to give product **8** bearing a free amino group with intact chiral centers with a 92% yield [Eq. (5)]. This process provides easy access to optically pure *meta*-indoline-substituted anilines that are not easily obtained by cross-coupling or Friedel–Crafts reactions.



In summary, we have demonstrated the organocatalytic asymmetric arylative dearomatization of indole derivatives through two tandem approaches involving 2,3-disubstituted indoles and QIKs. One approach employed an enantioselective cascade 1,4 addition/alcohol elimination reaction, the

other utilized a one-pot tandem arylative dearomatization/transfer hydrogenation sequence. In both cases, enantiomerically pure indole derivatives that bear an all-carbon quaternary stereogenic center were generated in high yields and excellent stereoselectivities (all d.r. > 95:5, up to 99% *ee*). Furthermore, these reactions utilized QIKs as latent aromatic rings to accomplish regio- and stereoselective arylative dearomatizations, which not only serve as successful examples for enantioselective transformations involved QIKs, but also provide an efficient strategy to access optically pure *meta*-indoline-substituted anilines.

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[13] CCDC 1020908 (**3ea**) and 1020909 (**7aa**) contain the supplementary crystallographic data for this paper (see the Supporting Information for details). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

