Organocatalysis

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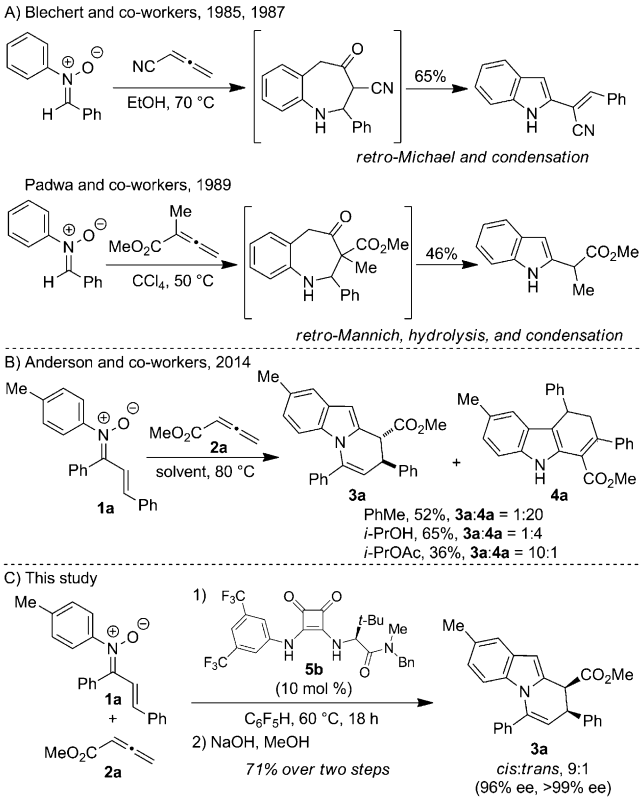
Catalytic Asymmetric Synthesis of Dihydropyrido[1,2-*a*]indoles from Nitrones and Allenoates

*Wiktoria H. Pace, Dong-Liang Mo, Tyler W. Reidl, Donald J. Wink, and Laura L. Anderson**

Abstract: *An asymmetric method for the synthesis of dihydropyrido[1,2-a]indoles from mixtures of nitrones and allenoates has been developed. This transformation showcases the use of squaramide catalysis in a complicated cascade system that has been shown to be highly sensitive to reaction conditions and substituent effects. The new method provides access to enantiomerically enriched dihydropyridoindoles from modular, non-indole reagents. The optimization and scope of the new transformation is discussed in addition to initial mechanistic experiments that indicate the role of the catalyst.*

The addition and rearrangement reactivity of nitrones and allenes has been studied for the synthesis of a variety of different heterocycles.[1] The research groups of Blechert and Padwa independently reported that the treatment of *N*-aryl nitrones with allenoates can provide access to benzazepine intermediates that undergo either retro-Michael or retro-Mannich ring opening to give 2-vinyl indole or 2-alkyl indole products, respectively, depending on the substitution pattern of the allene (Scheme 1 A).[1a–f] Recently, our group observed that solvent effects play a major role in determining whether mixtures of *N*-aryl nitrones and allenoates give dihydrocarbazole or dihydropyridoindole products (Scheme 1 B).[2] These examples serve to illustrate the appealing versatility of these types of cascade reactions for the preparation of heterocycles, as well as the challenges associated with controlling these processes, which are highly sensitive to reaction conditions and substituent effects.[1j] Herein we describe the development of the first catalytic asymmetric version of these cascade reactions and our discovery of appropriate conditions to provide access to dihydropyrido[1,2-*a*]indoles in good yield with high diastereoselectivity and excellent enantioselectivity (Scheme 1 C). Dihydropyrido[1,2-*a*]indoles are important scaffolds found in a variety of natural products and biologically active molecules.[3] Methods for accessing these heterocyclic structures are usually limited to the functionalization of indoles or indolines, and often require multistep procedures for the installation of the fused piperidine ring.[4] The method described herein provides an efficient modular alternative for the asymmetric synthesis of dihydropyrido[1,2-*a*]indoles.

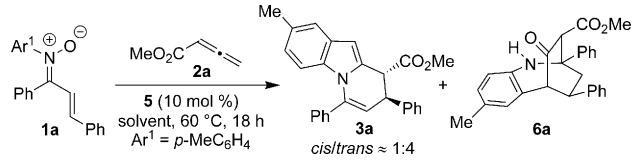


Scheme 1. Cascade reactions of nitrones and allenes for heterocycle synthesis. Bn = benzyl.

Several thiourea and squaramide catalysts were tested for the asymmetric conversion of nitrone **1a** and allenoate **2a** into dihydropyridoindole **3a** on the basis of the efficient racemic synthesis of **3a** with 1,3-bis(3,5-bistrifluoromethylphenyl)thiourea.[2] The treatment of a mixture of **1a** and **2a** with thiourea **5a** (10 mol %) at 60 °C provided **3a** in 12 % yield with poor enantioselectivity as a mixture with heterocycle **6a** (Table 1, entry 1).[5] Elevation of the reaction temperature did not increase the yield of **3a**. In contrast, the analogous squaramide catalyst **5b** gave **3a** in 49 % yield with moderate enantioselectivity (Table 1, entry 2). Larger amide substituents on the squaramide catalyst, as shown for **5c**, had little effect on the yield of the reaction but led to a decrease in the enantioselectivity of the process (Table 1, entry 3). Although similar squaramide catalysts are known, **5b** and **5c** have not yet been reported.[6] Similar reactivity trends correlating with an increase in the size of the amide substituent have been observed previously.[6c] Owing to the successful use of amine-tethered thiourea and squaramide catalysts for Michael addition and Diels–Alder reactions,

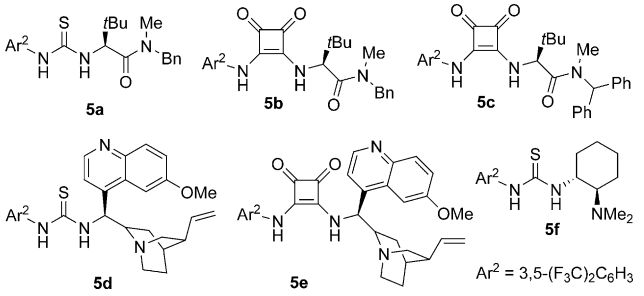
[*] W. H. Pace, Dr. D.-L. Mo, T. W. Reidl, Dr. D. J. Wink, Prof. L. L. Anderson
Department of Chemistry, University of Illinois at Chicago
845 West Taylor Street, Chicago, IL 60607 (USA)
E-mail: lauralin@uic.edu
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201602568.

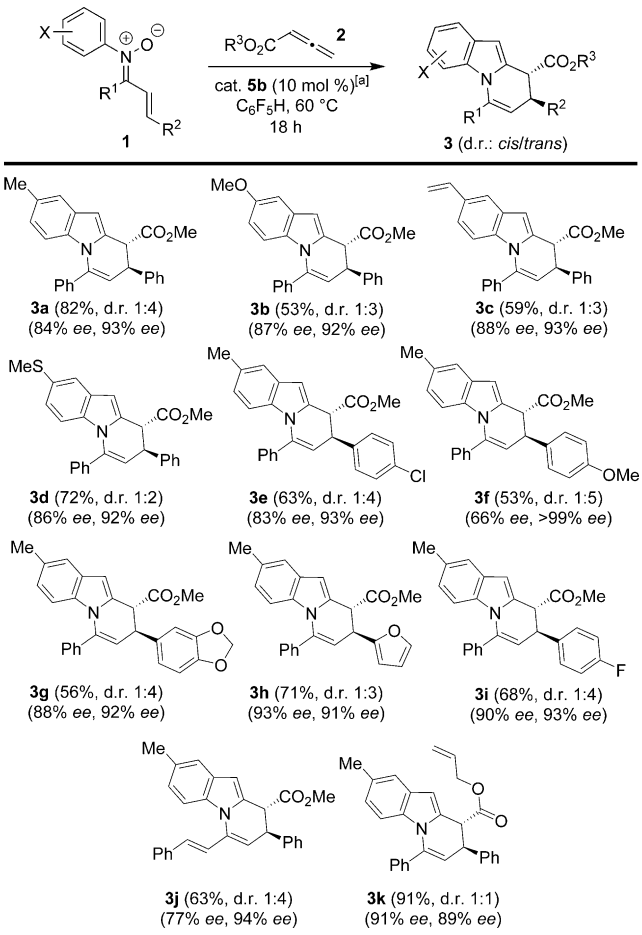
Table 1: Optimization of the asymmetric dihydropyridoindole synthesis.



Entry[a]	Catalyst	Solvent	Yield [%]		*ee* [%]
			3a	**6a**	**3a** (*cis*, *trans*)
1	**5a**	PhMe	12	47	35, 45
2	**5b**	PhMe	49	–	52, 81
3	**5c**	PhMe	50	30	70, 30
4	**5d**	PhMe	–	42	–
5	**5e**	PhMe	–	46	–
6	**5f**	PhMe	–	33	–
7	**5b**	C_6F_5H	67	–	81, 92
8	**5b**	$(F_3C)C_6H_5$	60	–	71, 88
9	**5b**	$CHCl_3$	46	25	24, 82
10	**5b**	C_6F_6	57	27	74, 96
11	**5b**	C_6F_5H[b]	82	–	84, 93
12	**5b**	C_6F_5H[c]	63	–	30, 70

[a] Reaction conditions: **1a** (1 equiv), **2a** (4–5 equiv), **5** (10 mol%), 0.1 M in solvent, 18 h. [b] Na_2SO_4 (1 equiv) was added. [c] $MgSO_4$ (1 equiv) was added.





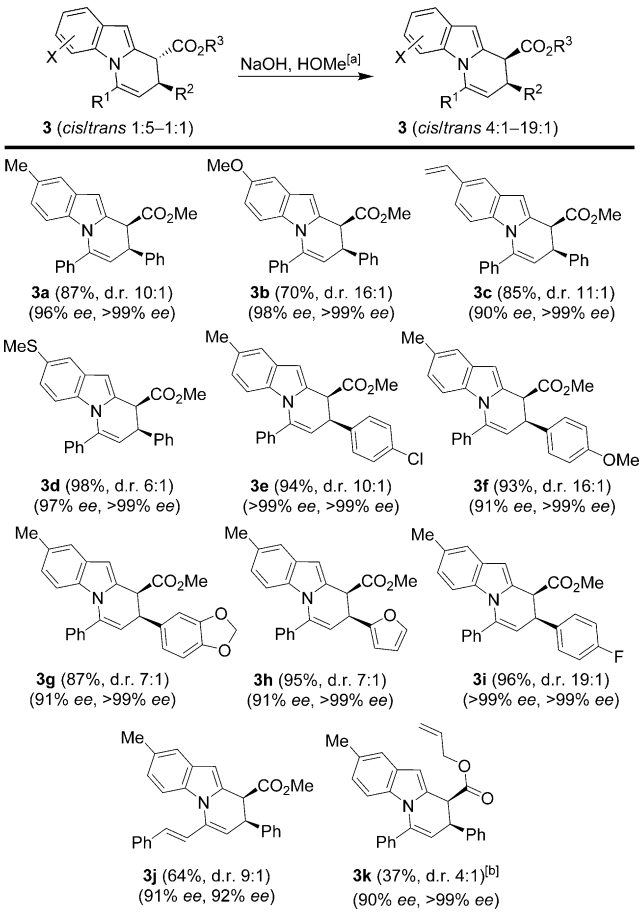
Scheme 2. Scope of the asymmetric dihydropyrido[1,2-*a*]indole synthesis. [a] Reaction conditions: **1** (1 equiv), **2** (4–5 equiv), Na_2SO_4 (1 equiv), 0.1 M in C_6F_5H.

catalysts **5d–f** were also tested for the cascade synthesis of **3a** from **1a** (Table 1, entries 4–6).[7] Surprisingly, these reaction mixtures all favored the formation of **6a**.[8]

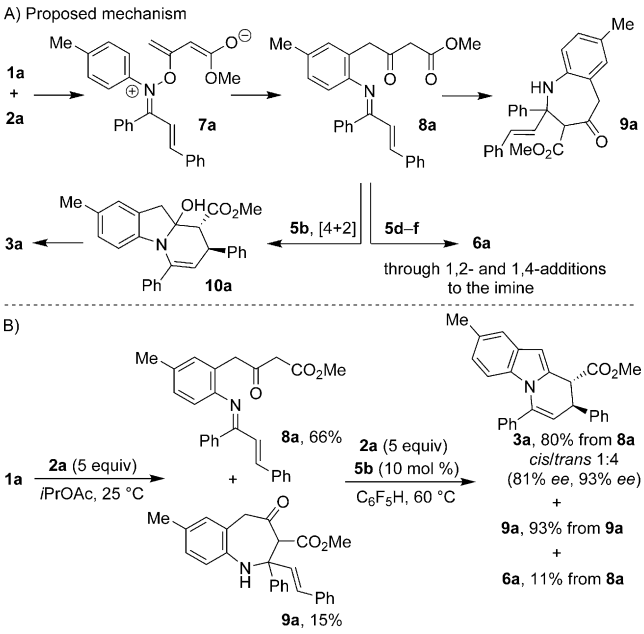
Since the squaramide catalyst **5b** provided the best initial yield and enantioselectivity for the synthesis of **3a** from **1a** and **2a**, further optimization was pursued with this scaffold. Appropriate selection of the reaction solvent was most effective in increasing both the yield and enantioselectivity of **3a** (Table 1, entries 7–10). The most efficient solvent for the asymmetric preparation of **3a** was determined to be C_6F_5H. The addition of Na_2SO_4 to the reaction mixture further increased the yield and enantioselectivity, unlike $MgSO_4$, which had no advantageous effect (Table 1, entries 11 and 12). Product **3a** was formed with 1:4 *cis*/*trans* diastereoselectivity under all of the conditions described in Table 1. Decreased reaction times favored the *trans* isomer in attenuated yields. Further investigation of the scope of the asymmetric dihydropyridoindole synthesis was pursued with the conditions shown in Table 1, entry 11.

The scope of the dihydropyridoindole synthesis was tested by varying the substitution patterns of nitrone **1** and allenoate **2**. Both electron-donating substituents and alkyl groups were tolerated at the *N*-aryl functionality of nitrone **1** (products **3a–d**; Scheme 2). Several different aryl and heteroaryl substituents were also tolerated at the β-position of the nitrone, including Cl-, F-, and MeO-substituted arenes, a protected catechol, and furan (products **3e–i**). Crystallization of **3e** and analysis by X-ray diffraction showed that the absolute configuration of the dihydropyridoindole is as illustrated. The electrophilic position of the nitrone proved to be more sensitive to electronic effects than the β-position; however, a styrenyl substituent was tolerated in this position, as well as a phenyl substituent (product **3j**). Variation of the allenyl ester substituent was also tolerated, and pyridoindole **3k** was isolated in good yield with good enantioselectivity.

Epimerization methods were investigated for the conversion of *cis*/*trans* mixtures of dihydropyridoindoles **3** into the thermodynamically favored isomer. The treatment of a 1:4 *cis*/*trans* mixture of **3a** with a solution of NaOH in MeOH gave high conversion into a 9:1 mixture in favor of the thermodynamically favored *cis* isomer (Scheme 3). This epimerization process also exhibited a slight amplification of enantiomeric excess, possibly as a result of diastereomeric interactions between the different isomers of the enantiomerically enriched substrate in the presence of the base.[9–11] The majority of the products shown in Scheme 2 similarly underwent this epimerization reaction to provide **3** with d.r. > 8:1 in favor of the *cis* diastereomer and with excellent enantioselectivity. Thioether **3d**, catechol-substituted **3g**, and



Scheme 3. Epimerization to the *cis* isomer. [a] Reaction conditions: 0.1 M NaOH in MeOH, 25 °C, 1 h. [b] The reaction was carried out with 0.1 M NaOH in allyl alcohol.



Scheme 4. Investigation of the role of catalyst **5b**.

furan-substituted **3h**, were converted into mixtures favoring the *cis* isomer with somewhat attenuated diastereoselectivity. Since these epimerization conditions also promote transesterification, the epimerization of **3k** was carried out in allyl alcohol. Through a two-step process incorporating an asymmetric cascade reaction followed by an epimerization, a variety of dihydropyridoindoles were prepared efficiently from simple nitrone and allenoate reagents with high diastereoselectivity and excellent enantioselectivity.

To gain some insight as to the role of catalyst **5b** in controlling the chemo- and enantioselectivity of the dihydropyridoindole synthesis, we carried out several mechanistic experiments. To determine whether **5b** functioned as an asymmetric epimerization catalyst for dihydropyridoindole products **3**, a racemic mixture of **3a** was treated with **5b** (10 mol%) under the optimal reaction conditions.[12] Only a minor increase in the *ee* value of **3a** was observed in the presence of **5b**, which suggests that catalyst **5b** controls the enantioselectivity of the dihydropyridoindole synthesis through interaction with one of the intermediates in the cascade process.

A proposed mechanism for the cascade reaction is shown in Scheme 4A. The addition of **1a** to the electrophilic position of **2a** could initiate C–C bond formation to form enaminoketone **8a**, which could undergo a Mannich addition to form benzazepine **9a** or a [4+2] cycloaddition to form dihydropyridoindole **3a** after the elimination of water from **10a**. Through a complementary pathway, enaminoketone **8a** could also undergo a series of intramolecular Mannich and Michael addition steps to form **6a**. Considering that both the chemoselective and enantiodetermining steps of the proposed cascade mechanism occur after the formation of the enaminoketone **8a**, we decided to examine the effect of catalyst **5b** when added to a solution of enaminoketone **8a**. A mixture of **8a** and benzazepine **9a** was generated in the absence of a catalyst when **1a** and **2a** were mixed at ambient temperature in isopropyl acetate.[2] This mixture was then transferred to C_6F_5H and exposed to catalyst **5b**. When a 5:1 mixture of **8a** and **9a** was treated with catalyst **5b** under the optimal reaction conditions (Scheme 4B), the results were consistent with those observed when a mixture of **1a** and **2a** was exposed to catalyst **5b** under identical conditions. Similarly, when a mixture of **8a** and **9a** was treated with catalyst **5d**, a mixture of **6a** and **9a** was isolated.[13] In both experiments, the benzazepine intermediate **9a** was not converted into either **3a** or **6a**, which suggests that the formation of **9a** is irreversible. These experiments indicate that the catalyst controls both the chemoselectivity and the enantioselectivity of the transformation through its interaction with the enaminoketone intermediate **8a**.

In summary, we have determined conditions for the asymmetric synthesis of dihydropyrido[1,2-*a*]indoles from mixtures of *N*-aryl α,β-unsaturated nitrones and allenoates through an asymmetric cascade sequence guided by chiral squaramide catalysts. This transformation shows similar tolerance to our initial discovery of the racemic version of this transformation. High enantioselectivity was observed for the formation of predominantly *trans* dihydropyridoindoles as well as the corresponding *cis* products accessed through subsequent epimerization. Initial mechanistic experiments

suggest that catalyst control of product selectivity and enantioselectivity occurs after initial N–O bond cleavage and attachment of the allenoate fragment to the *N*-aryl group. This method provides efficient access to enantiomerically enriched dihydropyrido[1,2-*a*]indoles from non-indole starting materials and is the first catalytic asymmetric cascade process of this type.

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Keywords: allenes · cascade reactions · heterocycles · nitrones · squaramides

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[8] The structure of **6a** was determined by the crystallization and X-ray crystal-structure analysis of an analogue with a *p*-methoxyphenyl substituent. See the Supporting Information for details.

[9] The increase in the *ee* value during the epimerization of *trans*-**3** to *cis*-**3** is an unusual phenomenon that is plausible in the chiral nonracemic environment of the substrate, which could produce diastereomeric interactions during potential epimerization pathways, such as ester enolization or C–C bond cleavage through donation from the N atom. For related examples of the amplification of enantiomeric excess as a result of substrate interactions, see: a) M. Mauksch, S. B. Tsogoeva, I. M. Martynova, S. Wei, *Angew. Chem. Int. Ed.* **2007**, *46*, 393–396; *Angew. Chem.* **2007**, *119*, 397–400; b) K. Soai, T. Shibata, I. Sato, *Acc. Chem. Res.* **2000**, *33*, 382–390; c) H. Lange, R. Huenerbein, R. Fröhlich, S. Grimme, D. Hoppe, *Chem. Asian J.* **2008**, *3*, 78–87.

[10] Experiments repeated on a different HPLC instrument and a column with a chiral stationary phase indicate that these observations are instrument-independent.

[11] When racemic *trans*-**3a** was mixed with **3a** (*cis*/*trans* 10:1, 96% *ee*, >99% *ee*; 20 mol%) and subjected to epimerization conditions, *trans*-**3a** was enantiomerically enriched by 18% *ee* after 28% conversion (see the Supporting Information). This experiment supports the asymmetric amplification observed during the epimerization reactions in Scheme 3.

[12] See the Supporting Information for details.

[13] See the Supporting Information for the complementary experiment with catalyst **5d**.

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