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Enantioselective Desymmetrization of *para*-Quinamines through an Aminocatalyzed Aza-Michael/Cyclization Cascade Reaction

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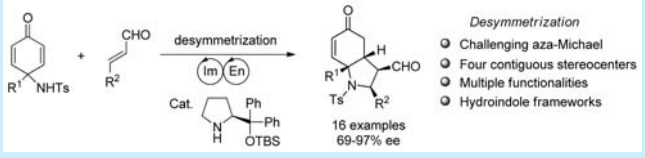
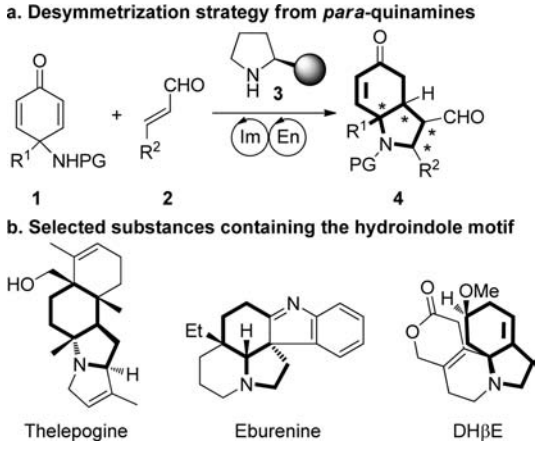
Supporting Information

ABSTRACT: An unprecedented organocatalytic asymmetric desymmetrization of *para*-quinamines leading to functionalized hydroindoles, a common motif in many alkaloids, has been reported. The ability of diarylprolinol silyl ethers to promote iminium and enamine activation of α,β-unsaturated aldehydes in one catalytic cycle is the centerpiece of the strategy involving a challenging aza-Michael/intramolecular cyclization cascade reaction. A range of prochiral *para*-quinamines and α,β-unsaturated aldehydes were investigated to afford 16 examples of hydroindoles possessing four contiguous stereocenters including one quaternary carbon. The hydroindole structures include multiple orthogonal functionalities, which underwent various transformations.



Desymmetrization processes are powerful means of transforming prochiral or *meso*-molecules into functionalized enantioenriched compounds.[1] Among the vast array of substrates available for such transformations, cyclohexadienone systems contain a rigid six-membered ring and functionalities, which are attributes that make dienones attractive starting materials to reach complex cyclic architectures via a desymmetrization process.[2] The chief challenge facing the organic chemists within this field lies in the use of a catalyst enabling the discrimination between two enantiotopic atoms or groups during the symmetry-breaking transformation. Despite the hurdles, significant achievements have emerged in the asymmetric desymmetrization of cyclohexadienone substrates.[2] Besides transition metal catalysis, the ability of asymmetric organocatalysis to promote a wide range of synthetic transformations has been successfully exploited to promote the desymmetrization of dienone systems. For instance, prolinol silyl ethers,[3] *N*-heterocyclic carbenes,[4] *cinchona*-derived thiourea,[5] phase transfer catalysts,[6] or phosphoric acids[7] turned out to be suitable catalytic systems. While several reports have described desymmetrization processes for which the nucleophile that attacks the dienone is already attached to the cyclohexadienone motif, bimolecular transformations have received less attention. In an important contribution to this field, the group of Rovis reported an asymmetric desymmetrization of peroxyquinols in the presence of aliphatic and aryl aldehydes using a Brønsted acid-catalyzed acetalization and intramolecular oxa-Michael cascade reaction.[7b] Other contributions by the groups of Johnson,[3c] Wang,[8] and Fan[9] have outlined the ability of cyclohexadienone motifs to give complex cyclic architectures via bimolecular transformations. Despite these recent advances, to the best of our knowledge a bimolecular asymmetric organocatalyzed desymmetrization strategy starting from *para*-quinamines **1** (4-amino-4-alkyl-2,5-cyclohexadienones) has never been reported, while new advances in this area could pave the way to new nitrogen-containing heterocycles (Scheme 1).

Scheme 1. Desymmetrization Towards Hydroindoles



As part of our ongoing research into the development of organocatalytic methodologies,[10] we wish to report herein the implementation of a novel dissymmetrical construction of functionalized nitrogen-containing polycycles via an aza-Michael/cyclization cascade reaction. The ability of chiral secondary amines to promote iminium and enamine activation of α,β-unsaturated aldehydes **2** in one catalytic cycle will be the centerpiece of the desymmetrization strategy toward hydroindole structures. This is a common motif in natural substances and biorelevant compounds such as the alkaloids thelepogine,[11] eburenine,[12] and dihydro-β-erythroidine (DHβE).[13] Central to the implementation of the desymmetrization is the addition of *para*-quinamines **1** to α,β-unsaturated aldehydes **2**. Amino-catalyzed aza-Michael additions have been extensively studied in

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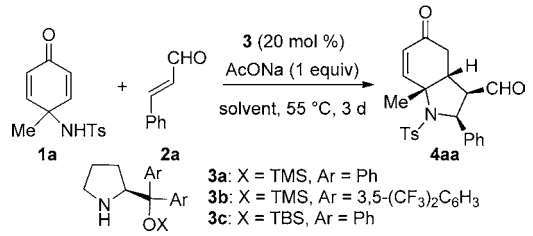
the literature, but some challenges still require additional efforts to extend this reaction in synthetically interesting new directions.[14] In particular, the use of hindered amines in intermolecular aza-Michael reactions remains scarce in the literature thus limiting the substrate scope to more reactive amines such as hydroxylamine derivatives or nitrogen-containing heterocycles. In addition, the reversibility inherent to the addition of an amine onto iminium species, the amine nucleophile/aminocatalyst competition toward addition and the intermolecular nature of the strategy are potential difficulties to embark on the reaction of *para*-quinamines **1** with *α,β*-unsaturated aldehydes **2**. Nevertheless, recent breakthroughs in aza-Michael reactions with amines catalyzed by diarylprolinol silyl ethers **3** and AcONa were a driving force to investigate the desymmetrization depicted in Scheme 1.[15]

Table 1. Reaction Optimization[a]

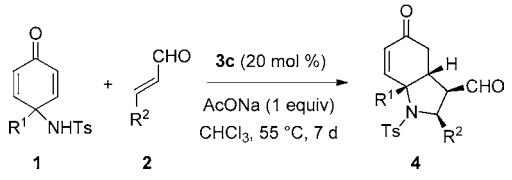


entry	3	solvent	% yield[b]	dr[c]	% ee[d]
1	**3a**	$CHCl_3$	60	4:1	92
2	**3b**	$CHCl_3$	n.r.	n.d.	n.d.
3	**3c**	$CHCl_3$	80	3:1	96
4[e]	**3c**	$CHCl_3$	57	4:1	95
5[f]	**3c**	$CHCl_3$	65	2:1	95
6	**3c**	toluene	50	2:1	92
7	**3c**	DMF	<10	n.d.	n.d.
8	**3c**	MeCN	20	3:1	97

[a]Reactions were performed on 0.15 mmol scale using 1 equiv of **1a**, 1.5 equiv of **2a**, 20 mol % of **3**, and 1 equiv of AcONa at 55 °C for 3 days unless otherwise noted. n.r. = no reaction. n.d. = not determined. [b]Isolated yield for the major diastereomer. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude. The structure of each diastereomer has been determined by full analyses; see Supporting Information for further studies. [d]Enantiomeric excesses were determined by chiral HPLC on the Wittig products prepared from major diastereomers. See Supporting Information. [e]One equivalent of AcOH was used instead of AcONa. [f]No AcONa was added to the reaction mixture.

We began our investigation by studying the reaction of the readily available *para*-quinamine **1a** with *trans*-cinnamaldehyde **2a** in the presence of diarylprolinol silyl ether catalysts **3** and AcONa (Table 1).[16] The tosyl nitrogen protecting group of **1a** is essential to the success of the reaction.[17] For instance, acetyl or *tert*-butoxycarbonyl groups shut down the reactivity of the *para*-quinamines because these groups rendered the NH less acidic for a subsequent deprotonation under basic conditions.[15b] Starting from **1a**, various diarylprolinol silyl ether catalysts **3** were investigated (entries 1−3).[18] The catalyst **3a** provided the desired product **4aa** in 60% isolated yield and 92% *ee* for the major diastereomer, while no reaction occurred by using the 3,5-$(CF_3)_2C_6H_3$-derived catalyst **3b** (entries 1 and 2). In order to improve the yield, we surmised that the presence of a bulkier silyl group (e.g., TBS) could improve the stability and lifetime of the catalyst.[10b] Therefore, the best result was obtained with **3c**, which gave rise to **4aa** in 80% yield and 96% *ee* (entry 3). Experiments carried out under acidic conditions (entry 4) or neutral conditions (entry 5) gave lower yields of **4aa**. The influence of the reaction medium was then investigated by screening various solvents (entries 6−8). While toluene turned out to be a suitable solvent for the desymmetrization process (**4aa**, 50% yield), switching to DMF or MeCN was detrimental to the formation of **4aa**. With the optimized conditions in hand (Table 1, entry 3), the scope and limitations with respect to the nature of R^1 and R^2 were assessed (Table 2). A reaction time of 7 days was required to ensure maximum conversion rates and optimal yields. Initially, changes to the R^2 group on the *α,β*-unsaturated aldehydes **2** were investigated (**2a−m**). We first focused our attention on the influence of the position of the aromatic substituent on the efficiency and stereoselectivities of the reaction. Starting from aldehydes **2b** and **2e** bearing a methyl or a methoxy group in para-position, similar results as for **4aa** were obtained even if a slight decrease of *ee* was observed for **4ae** (entries 1, 2, and 5). For the methyl and methoxy series, the reaction rate starting from **1a** is in the order para > meta > ortho with similar levels of stereoselectivities within each series (entries 2−7). This reactivity order could be explained by an increased steric hindrance at the *β* position of the enal thus hampering the nucleophilic addition of the *para*-quinamine **1a**. Substrates **2h** and **2i** possessing a halogen group also reacted to afford the desired hydroindoles **4ah** and **4ai** in 61% and 51% yield, respectively, with good diastereoselectivities and high enantioselectivities (entries 8 and 9). Surprisingly, a slight decrease of reactivity (27−30% yield) was observed starting from *α,β*-

Table 2. Substrate Scope[a]



entry	R^1	R^2	4	% yield[b]	dr[c]	% ee[d]
1[e]	Me (**1a**)	Ph (**2a**)	**4aa**	80	3:1	96
2	Me (**1a**)	4-MeC_6H_4 (**2b**)	**4ab**	76	5:1	93
3	Me (**1a**)	3-MeC_6H_4 (**2c**)	**4ac**	65	5:1	93
4	Me (**1a**)	2-MeC_6H_4 (**2d**)	**4ad**	50	4:1	92
5	Me (**1a**)	4-$MeOC_6H_4$ (**2e**)	**4ae**	71	5:1	81
6	Me (**1a**)	3-$MeOC_6H_4$ (**2f**)	**4af**	61	5:1	n.d.
7	Me (**1a**)	2-$MeOC_6H_4$ (**2g**)	**4ag**	43	5:1	88
8	Me (**1a**)	4-ClC_6H_4 (**2h**)	**4ah**	61	4:1	92
9	Me (**1a**)	4-FC_6H_4 (**2i**)	**4ai**	51	5:1	93
10	Me (**1a**)	4-$NO_2C_6H_4$ (**2j**)	**4aj**	30	2:1	97
11	Me (**1a**)	2-$NO_2C_6H_4$ (**2k**)	**4ak**	27	4:1	90
12	Me (**1a**)	2-thienyl (**2l**)	**4al**	63	5:1	86
13	Me (**1a**)	Me (**2m**)	**4am**	42	4:1	69
14	Et (**1b**)	Ph (**2a**)	**4ba**	24	2.5:1	88
15	Bu (**1c**)	Ph (**2a**)	**4ca**	13	2:1	90
16	Ph (**1d**)	Ph (**2a**)	**4da**	61	5:1	93

[a]Reactions were performed on 0.15 mmol scale using 1 equiv of **1**, 1.5 equiv of **2**, 20 mol % of **3c**, and 1 equiv of AcONa at 55 °C for 7 days unless otherwise noted. n.d. = not determined. [b]Isolated yield for the major diastereomer. [c]Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude. [d]Enantiomeric excesses were determined by chiral HPLC on the Wittig products prepared from major diastereomers **4**. See Supporting Information for details. [e]In this case, the reaction mixture was stirred for 3 days.

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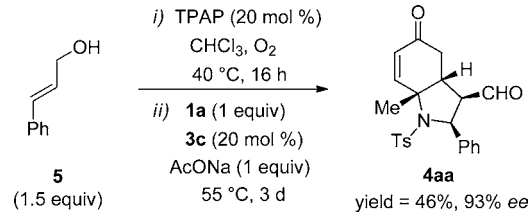
unsaturated aldehydes **2j** and **2k** bearing a nitro substituent on the aromatic ring (entries 10 and 11). The thiophene-derived enal **2l** was found to undergo a clean reaction with *para*-quinamine **1a** to provide the product **4al** in 63% yield and 86% *ee* (entry 12). Crotonaldehyde **2m** was also amenable to the desymmetrization reaction providing access to **4am** in 42% yield with 69% *ee* (entry 13). Variations to the prochiral scaffold were next investigated (entries 14 and 15). The rate decreased rapidly with the increase of the chain R^1 length for similar reasons as described above. While the reaction of **1b** bearing an ethyl group afforded **4ba** in 24% yield and 88% *ee*, the butyl-derived product **4ca** was prepared in a modest yield of 13% with high enantiocontrol (90% *ee*). An increase of the yield was observed by reacting **2a** with **1d** bearing a phenyl group. The product **4da** was obtained in 61% yield and 93% *ee* (entry 16).

From a synthetic standpoint, the in situ preparation of aldehydes is particularly interesting due to their sensitivity to storage and possible degradation over time. To this aim, the desymmetrization strategy has then been combined with a Ru-catalyzed aerobic oxidation of allylic alcohols through a multicatalytic sequential approach (Scheme 2).

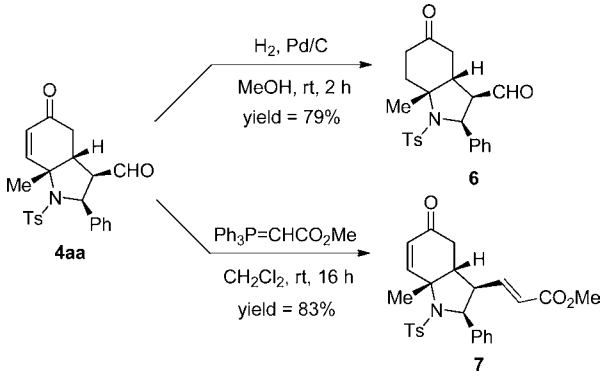
Scheme 2. Multicatalytic Oxidation and Organocatalytic Desymmetrization Sequence



The oxidation of cinnamyl alcohol **5** in the presence of tetrapropylammonium perruthenate (TPAP)[19] and O_2 produced the corresponding *trans*-cinnamaldehyde **2a**, which was in situ converted to **4aa** in 46% yield and 93% *ee* after subsequent addition of *para*-quinamine **1a**, catalyst **3c**, and AcONa. To illustrate the synthetic potential of bicyclic structures **4**, selective transformations were carried out (Scheme 3). Hydrogenation of **4aa** furnished the perhydroindole **6** in a 79% yield and functionalization of the aldehyde via a Wittig reaction gave rise to **7** in 83% yield.

In conclusion, we have described the first example of aminocatalyzed desymmetrization of *para*-quinamines toward the enantioselective synthesis of hydroindole motifs, widely found in alkaloids. Key features of our strategies include a challenging aminocatalyzed aza-Michael reaction and an iminium/enamine cascade process mediated by a diphenylprolinol TBS ether catalyst in the presence of sodium acetate. Sixteen examples of hydroindoles were prepared (13−80%) with enantiomeric excesses ranging from 69% to 97%. A noteworthy feature of this transformation lies in the formation of four contiguous stereocenters including one quaternary carbon. The original desymmetrization process was combined with a Ru-catalyzed oxidative process to outline the synthetic potential of the strategy leading to hydroindole motifs, which can undergo various transformations.

Scheme 3. Transformations of Product 4aa



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data including NMR spectra and relevant HPLC traces. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01595.

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Notes

The authors declare no competing financial interest.

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