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Organocatalytic Atroposelective Formal Diels–Alder Desymmetrization of *N*-Arylmaleimides

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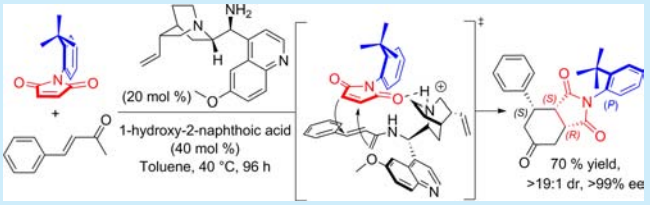
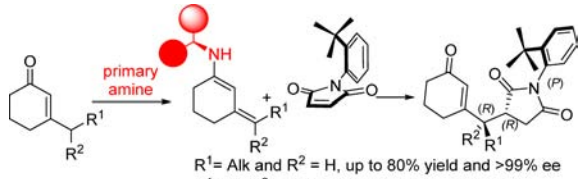
Supporting Information

ABSTRACT: The atroposelective desymmetrization of *N*-arylmaleimides was realized by means of a primary amine catalyzed Diels–Alder reaction of enones. The chiral axis as new element of chirality is generated under the remote control of the catalyst that selectively drives the formal Diels–Alder reaction through an exclusive stereochemical outcome.



Recent applications of organocatalysis to the synthesis of atropisomers[1] have demonstrated the great advances reached by this important branch of catalysis. Since the seminal report by Zhu on the atroposelective synthesis of cyclophanes through an intramolecular cycloetherification catalyzed by chiral quaternary ammonium salt,[2] different reactions that control the chirality of stereogenic axis have been realized using various organocatalytic strategies.[3] Recently, our group reported the first synthesis of atropisomeric succinimides through the primary amine catalyzed vinylogous Michael addition–desymmetrization reaction of *N*-arylmaleimides (Scheme 1).[3i]

Scheme 1. Atroposelective Vinylogous Desymmetrization of *N*-(2-*tert*-Butylphenyl)maleimide



The Diels–Alder (DA) reaction stands out as one of the most explored reactions for the synthesis of cyclic compounds and has found many applications in organic chemistry.[4] Maleimides are one of the most powerful dienophiles, and the corresponding succinimides are precious products for biological and pharmaceutical applications.[5] However, organocatalytic enantioselective DA reactions of maleimides have been explored mainly using anthrone and with particular attention to the control of chiral centers but rarely a stereogenic axis.[6] In 2009, Melchiorre reported the highly stereoselective organocascade reaction of α,β-unsaturated ketones and *N*-aryl/benzylmaleimides catalyzed by a *Cinchona* alkaloid primary amine in which formal DA cycloadducts were formed.[7] Merging the ability of this organocatalyst[8] to activate enones and to realize atroposelective transformations,[3i] we present here the results on the atroposelective desymmetrization[9] of *N*-(2-*tert*-butylphenyl)maleimides through a DA reaction of α,β-unsaturated enamines.[10] The presence of a *tert*-butyl group on *N*-arylmaleimide **2a** restricts the rotation along the N–C_{Ar} single bond,[11,3i] giving rise to two nonequivalent faces of the plane of symmetry, which can be defined *atropotopic* (Scheme 2a). In fact, the substitution of one of the hydrogen atoms of the double bond with a different group engenders atropisomers since a stereogenic axis is revealed in the resulting molecule.[12] The *Re* and *Si* descriptors can be assigned to the atropotopic faces in analogy with the case of trigonal centers.[13] By arbitrarily viewing the maleimide **2a** from the right side (projection A) or from above after 90° rotation (projection B), the assignment of the following priority to the groups around the prochiral axis, *N* > *tert*-butyl > *o*-H_{Ar}, determines a clockwise rotation which defines this face as the *Re* face. In light of this definition, the central core of the desymmetrization reaction is the ability of catalyst to distinguish between the two *atropotopic Re* and *Si* faces of the maleimide while approaching the diene. In this way, it is possible to realize the cyclization process with a simultaneous generation of a stereogenic axis and three stereocenters (Scheme 2b).

Initially, we reacted (*E*)-4-phenylbut-3-en-2-one **1a** with *N*-(2-*tert*-butylphenyl)maleimide **2a** using 20 mol % of 9-amino(9-deoxy)-*epi*-hydroquinine **C** and 40 mol % of 2-hydroxybenzoic acid in toluene at 40 °C.

The desired succinimides were obtained as single diastereoisomers in good yield and excellent enantioselectivity (Table 1, entry 1). Among all the amines tested, 9-amino(9-deoxy)-*epi*-

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Scheme 2. Topic Relationships between Faces and Atoms of *N*-(2-*tert*-Butylphenyl)maleimide and Design Plan for the Desymmetrization Reaction

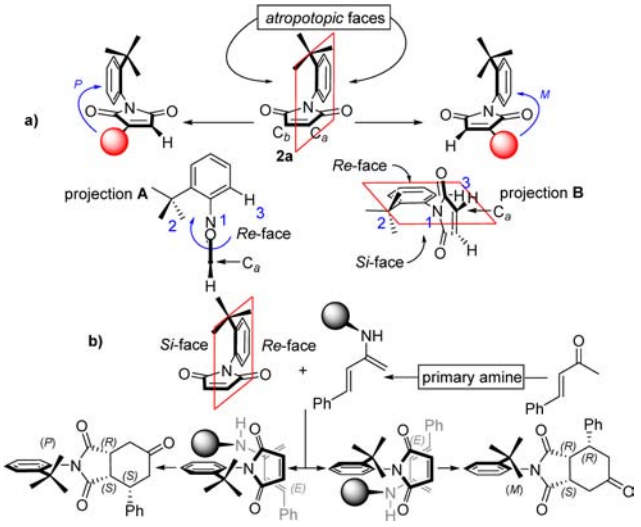
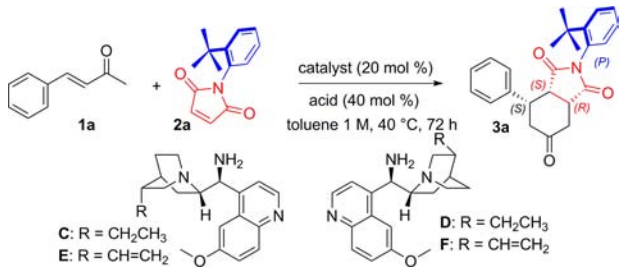


Table 1. Screening of the Reaction Conditions[a]

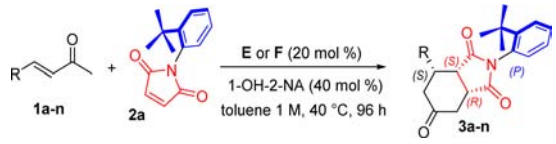


entry	catalyst	acid	**3a** yield[b] (%)	dr[c]	ee[d] (%)
1	**C**	2-OH-BA	61	>19:1	98
2	**D**	2-OH-BA	50	>19:1	97[g]
3	**E**	2-OH-BA	65	>19:1	>99
4	**F**	2-OH-BA	53	>19:1	>99[g]
5[e]	**E**	2-OH-BA	64	>19:1	>99
6[f]	**E**	2-OH-BA	64	>19:1	>99
7	**E**	CH_3COOH	40	>19:1	>99
8	**E**	$ClCH_2COOH$	33	>19:1	>99
9	**E**	$Cl_2CHCOOH$	20	>19:1	>99
10	**E**	2-NO_2-BA	53	>19:1	>99
11	**E**	4-NO_2-BA	27	>19:1	n.d.
12	**E**	2-F-BA	48	>19:1	98
13	**E**	2-I-BA	52	>19:1	>99
14	**E**	2-SH-BA	27	>19:1	>99
15	**E**	1-OH-2-NA	70	>19:1	>99

[a]Reactions performed with **1a** (0.4 mmol) and **2a** (0.2 mmol). [b]Isolated yield. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by HPLC on chiral stationary phase. [e]THF was used. [f]EtOAc was used. [g]*ent*-**3a** was obtained.

quinine **E** provided the highest yield and enantiocontrol and was employed to test different solvents and acidic cocatalysts (entries 2−4). Toluene was the optimal medium to conduct the reaction, and tetrahydrofuran (THF) and ethyl acetate (EtOAc) gave comparable results (entries 5 and 6). The use of acetic acid derivatives did not lead to high conversions (entries 7−9), so we focused on different benzoic acids and found that 1-hydroxy-2-naphthoic acid ensured the best results in terms of yields and enantioselectivity (entries 10−15). With the optimized reaction conditions identified, we explored the scope of different α,β-unsaturated ketones **1a−n** (Table 2,

Table 2. Scope of α,β-Unsaturated Ketone[a]



entry	catalyst	product	R	yield[b] (%)	dr[c]	ee[d] (%)
1	**E**	**3a**	Ph	70	>19:1	>99
2	**E**	**3b**	4-Cl-Ph	63	>19:1	>99
3	**F**	*ent*-**3b**	4-Cl-Ph	71	>19:1	>99
4	**E**	**3c**	3-Cl-Ph	58	>19:1	95
5	**E**	**3d**	3,4-Cl-Ph	65	>19:1	98
6	**E**	**3e**	4-F-Ph	48	>19:1	>99
7	**F**	*ent*-**3e**	4-F-Ph	75	>19:1	99
8	**E**	**3f**	4-NO_2-Ph	40	>19:1	>99
9	**E**	**3g**	4-OMe-Ph	45	>19:1	>99
10	**E**	**3h**	4-Me-Ph	46	>19:1	>99
11[e]	**E**	**3i**	3-OH-Ph	36	>19:1	99
12	**E**	**3j**	2-naphthyl	34	>19:1	>99
13	**E**	**3k**	thienyl	42	>19:1	>99
14	**F**	*ent*-**3k**	thienyl	50	>19:1	>99
15	**E**	**3l**	2-Br-Ph			
16	**E**	**3m**	pentyl			
17	**E**	**3n**	COOEt			

[a]Reactions performed with **1a−n** (0.4 mmol) and **2a** (0.2 mmol). [b]Isolated yield. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by HPLC on chiral stationary phase. [e]THF was used.

entries 1−17). Essentially, all α,β-unsaturated ketones gave the corresponding products in excellent diastereo- and enantioselectivity and in moderate to good yields. The presence of halogen atoms on the phenyl group of the ketone was well tolerated (entries 2−7), and electron-withdrawing or -releasing and heteroaromatic substituents gave the corresponding products in moderate yields (entry 8−13). Interestingly, the use of 9-amino(9-deoxy)-*epi*-quinidine **F** gave access to the opposite enantiomer of the cycloadducts (entries 3, 7, and 14). The reactivity was suppressed by an *o*-bromo substituent in the aryl group of the enone and also when an alkyl chain and an ester substituent were employed (entries 15−17).

We next examined the scope of different maleimides **2b−g**. As highlighted in Table 3, halogen and electrodonating groups proved ideal, ensuring good yields of product (entries 1−4). However, when a nitro group or a further *tert*-butyl substituent was employed, no conversion was observed, suggesting that spherical substituents placed below the horizontal plane of the maleimide hamper approach of the diene to the double bond (entry 5 and 6). Nevertheless, these reactions proceed in good yields and excellent enantioselectivity in the presence of a NHCbz group that can adopt different conformations (entries 7 and 8).[14] The absolute configuration of *ent*-**3o** has been determined to be *M*,3a*S*,7*R*,7a*R* by single-crystal X-ray diffraction analysis.[15]

The structure obtained allowed us to propose the ***endo*-TS-1** as the favored transition state (Scheme 3). According to our initial hypothesis, catalyst **F** selected exclusively the atropotopic *Si* face of **2b** by means of a hydrogen-bond interaction with the carbonyl group that accounts for the exclusive control over

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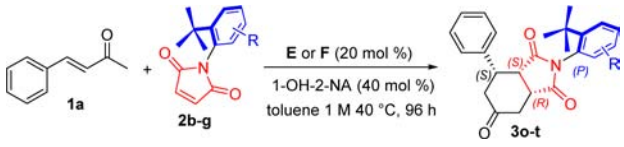
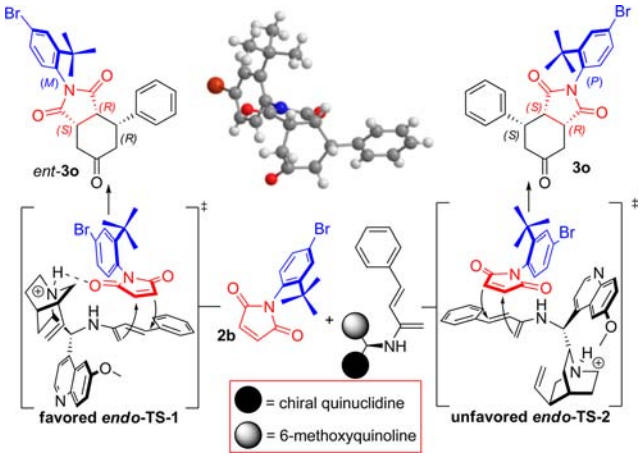
Table 3. Scope of Maleimide[a]



entry	catalyst	product	R	yield[b] (%)	dr[c]	ee[d] (%)
1[e]	E	**3o**	4-Br	50	>19:1	>99
2[e]	F	*ent*-**3o**	4-Br	47	>19:1	>99
3	F	*ent*-**3p**	4-Cl	71	>19:1	>99
4	E	**3q**	4-OMe	71	>19:1	>99
5	E	**3r**	5-NO_2			
6	E	**3s**	5-*t*-butyl			
7	E	**3t**	5-NHCbz	62	>19:1	94
8	F	*ent*-**3t**	5-NHCbz	55	>19:1	>99

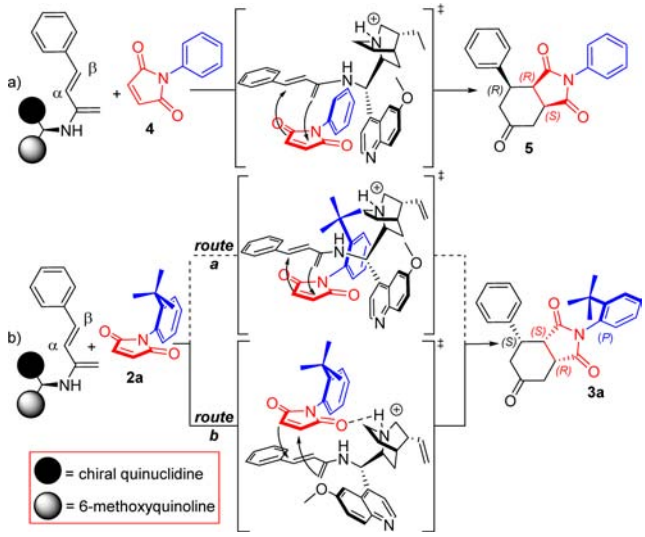
[a]Reactions performed with **1a** (0.4 mmol) and **2b–g** (0.2 mmol). [b]Isolated yield. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by HPLC on chiral stationary phase. [e]THF was used.

Scheme 3. X-ray Structure of *ent*-3o and Possible TS for the DA Desymmetrization with Catalyst F



central and axial chirality observed for *ent*-**3o**. The enantiomeric transition state ***endo*-TS-2** where the latter interaction was absent proved to be less favored. Interestingly, a comparison between compound **3a** and the analogue **5** prepared by Melchiorre[7] showed an opposite absolute configuration for the stereocenters even though **3a** and **5** were obtained from catalysts with the same absolute configuration (Scheme 4). Evidently, the presence of the *tert*-butyl substituent has a deep impact on the mechanism of the reaction highlighting the ability of the primary amine to adapt to the particular maleimide employed and preferentially drive the reaction through a site specific desymmetrization. In both reactions, the stereochemical outcome observed depends on the way that the α,β-unsaturated enamine and the maleimide approach each other. In the Melchiorre reaction (Scheme 4a) the stereochemistry obtained requires that the *Si* face of the diene C_β approaches the *Re* face of one of the maleimide's carbons. Despite the fact that in our reactions, no intermediates from the first Michael addition could ever be isolated, they always provide single diastereomers. Following the same tandem enamine–iminium ion sequence would result in the *tert*-butyl group bumping into the quinuclidine ring of the catalyst (Scheme 4b, route a). Thus, when **2a** is used, the α,β-

Scheme 4. Plausible Reaction Mechanisms for Maleimide 4 Pathway a and Maleimide 2a Pathway b



unsaturated enamine approaches from the maleimide side that is not shielded by the *tert*-butyl group (Scheme 4b, route b).

In conclusion, we have developed an organocatalytic atroposelective formal DA desymmetrization reaction for the synthesis of new succinimides bearing a chiral axis and three stereogenic centers. The desymmetrization highlights the role of 9-amino(9-deoxy)-*epi*-quinine in simultaneously controlling all of the elements of chirality and directing the reaction mechanism down a specific path. Calculations are in progress to provide further insights into the potential reaction mechanism.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; NMR, HPLC, and X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) The substitution of any atom of the five-membered cycle of **2a**, except nitrogen, generates axial chirality and can be defined as prochiral. The two carbon atoms of the double bond of **2a** are prochiral both for central and axial chirality, **Ca** is pro-M and **Cb** is pro-P.
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(14) The reactions were run for 96 h. Prolonged reaction times did not improve the conversions; thus, we believe that moderate yields were caused by deactivation of the catalytic system.
(15) CCDC-1044082 for *ent*-**3o**. See the Supporting Information

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