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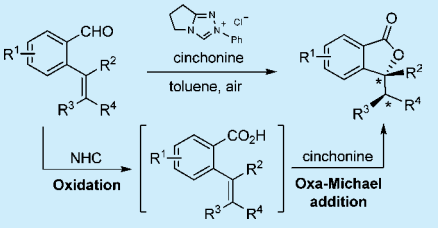
Asymmetric Domino Multicatalysis for the Synthesis of 3-Substituted Phthalides: Cinchonine/NHC Cooperative System

So Won Youn,* Hyoung Sub Song, and Jong Hyub Park

Department of Chemistry and Research Institute for Natural Sciences, Hanyang University, Seoul 133-791, Korea

Supporting Information

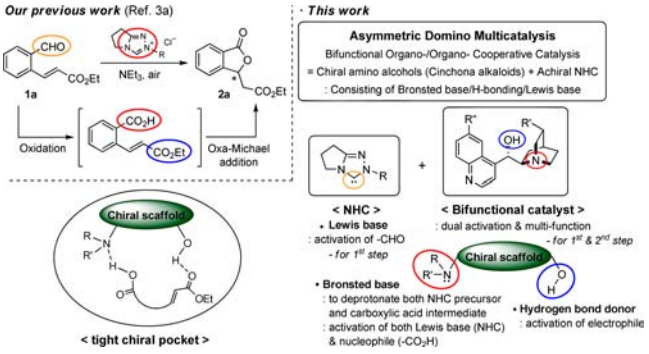
ABSTRACT: It is demonstrated that two organocatalysts, achiral NHC and chiral bifunctional cinchonine, are mutually compatible and operating concurrently and effectively to promote the asymmetric domino oxidation/oxa-Michael addition reaction. This protocol allowed access to both enantiomers of a product by using two natural, inexpensive pseudoenantiomeric cinchona alkaloids, cinchonine and cinchonidine, as well as to phthalides containing a chiral quaternary carbon center in good enantioselectivities.



Asymmetric domino multicatalysis[1,2] has been emerging as a highly efficient and powerful method for the synthesis of structurally complex molecules from relatively simple starting materials, obviating time/energy/cost-consuming unnecessary processes and allowing for outcomes that are not easily accessible with a single catalytic strategy. However, still relatively very few examples of this reaction have been reported due to two major challenges, catalyst compatibility and selectivity.

Recently, we reported an efficient N-heterocyclic carbene (NHC)-catalyzed domino oxidation/oxa-Michael addition reaction of 2-alkenylbenzaldehydes under aerobic conditions for the easy preparation of a wide range of 3-substituted phthalides bearing a C3-stereogenic center (Scheme 1, upper left-hand corner),[3a] which are versatile building blocks and privileged structural motifs found in a diverse array of compounds possessing important biological properties.[4] In this process, a 2-alkenylbenzoic acid intermediate resulting from NHC-catalyzed oxidation reaction of aldehyde functionality is seemingly formed,[5] followed by its intramolecular oxa-Michael addition reaction via deprotonation of $-CO_2H$ by a base and activation of alkene by coordination to the conjugate acid. During the course of this study, we also discovered that both a tight chiral pocket and the excess amount of base might be required for good stereocontrol and reactivity, respectively. Inspired by the intriguing report on NHC/Brønsted acid cooperative catalysis disclosed by the Rovis group,[2a,6] we reasoned that introduction of *a chiral acid catalyst* to the existing *achiral NHC catalyst* may result in a more efficient catalytic system for the electrophile activation via hydrogen bonding in asymmetric induction.[7] Since Brønsted base is also required to deprotonate not only a heterazolium salt but a $-CO_2H$ intermediate for generation of an NHC catalyst and a reactive nucleophile, respectively, the use of chiral bifunctional catalysts containing both amine and hydrogen bond donor moieties would significantly improve the efficiency of this proposed asymmetric domino multicatalysis, providing a tight chiral pocket (Scheme 1).

Scheme 1. Working Hypothesis of Asymmetric Domino Multicatalysis



Herein we disclose the realization of this proposal. The presence of both a basic quinuclidine tertiary amine and a free hydroxy group on C9 in cinchonine proved to be essential for the proper mode of catalyst action in this asymmetric transformation to give both reactivity and selectivity. *This is the first example involving a cooperative achiral NHC and chiral cinchona alkaloid catalytic system in asymmetric synthesis of 3-substituted phthalides.*[8] Noteworthy is that the formation of phthalides containing a chiral quaternary carbon center[9] could be achieved in good enantioselectivities. In addition, naturally occurring, inexpensive, unmodified two pseudoenantiomeric cinchona alkaloids, cinchonine and cinchonidine, allowed access to both enantiomers of a product in an enantioselective manner.

We began our studies on the proposed reaction using **1a** as the test substrate and examined the reaction parameters to identify optimal conditions (Table 1; for complete data, see the Supporting Information). Considering a couple of precedents to utilize quinuclidine derivatives to deprotonate heterazolium

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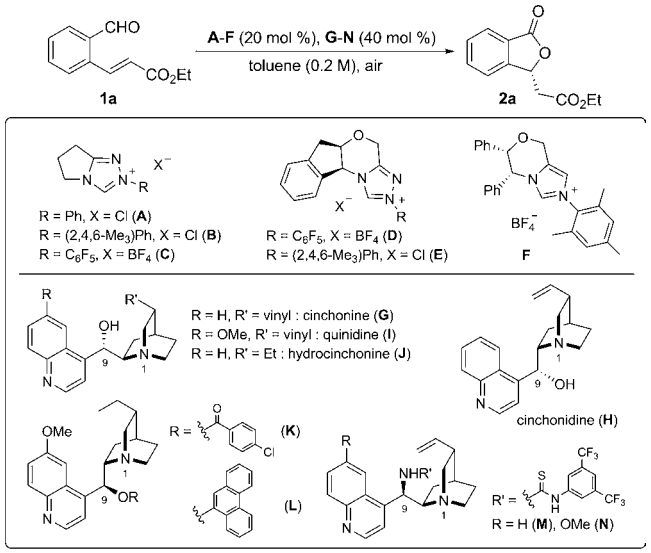
Table 1. Optimization Studies

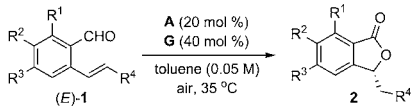


entry	NHC precursor	cocatalyst	temp (°C)	time (h)	yield (%)[a]	er[b]
1	**A**	**G**	60	24	97 (83)	82:18
2	**A**	**G**	35	72	70	84:16
3[c]	**A**	**G**	35	72	88 (72)	92:8
4	**B**	**G**	35	72	76	57:43
5	**C**	**G**	35	72	27	61:39
6	**D**	**G**	35	72	49	75:25
7	**E**	**G**	35	72	71	71:29
8	**F**	**G**	35	72	31	79:21
9	**A**	**H**	60	24	76	30:70
10	**A**	**I**	60	24	63	69:31
11[c]	**A**	**J**	35	72	86 (65)	90:10
12	**A**	**K**	60	24	54	50:50
13	**A**	**L**	35	72	36	51:49
14[c]	**A**	**M**	35	72	32	53:47
15[c]	**A**	**N**	35	72	33	58:42
16[c-d]	**A**	**G**	35	72	53	86:14
17[c, e]	**A**	**G**	35	72	76	87:13
18[c, f]	**A**	**G**	35	48	83 (70)	92:8

[a]Yields were determined by ^{1}H NMR using trichloroethylene as an internal standard. Value in parentheses indicates an isolated yield. [b]Enantiomeric ratio (er) was determined by chiral HPLC on a Daicel OD-H column. [c]In 0.05 M toluene. [d]Performed with 20 mol % cinchonine. [e]Performed with each 20 mol % of **A**, **G**, and NEt_3. Chemical yield (78%) and er (87:13) in the use of **G** and a carbene preformed from **A** and NEt_3 were very similar to those obtained from the addition of all together at once. [f]Under O_2 atmosphere (10 atm).

salts,[2i,10] we explored the effects of cinchona alkaloids which consist of both quinuclidine and hydrogen bond donor moieties and are well-known chiral catalysts for oxa-Michael addition reaction.[11,12] Much to our delight, the combination of triazolium salt **A** and cinchonine (**G**) without an additional base gave the desired product **2a** in good yield with a moderately high enantiomeric ratio (83%, er 82:18, entry 1). The use of either achiral or chiral NHCs in the presence of cinchonine resulted in the preferential formation of (*R*)-**2a** without any significantly beneficial effect of the use of chiral NHCs (entries 2 and 4−5 vs entries 6−8) as well as regardless of the NHC's chirality (entries 6−8). However, the structure of the NHC skeleton had affected the stereoselectivity to some extent (entries 2 and 4−8), suggesting that NHC takes part in the selectivity-determining cyclization step somehow. In general, significantly better reactivity and stereoselectivity were obtained

Table 2. Asymmetric Oxidative Cyclization Reaction of 2-Alkenylbenzaldehydes



entry	R^1	R^2	R^3	R^4	time (d)	yield (%)[a]	er[b]
1	H	H	H	CO_2Et (**1a**)	3	72 (**2a**)	92:8
2[c]	H	H	H	CO_2Et (**1a**)	6	76 (**2a**)	13:87
3[d-e]	H	H	H	CO_2Et ((*Z*)-**1a**)	2	43 (**2a**)	60:40
4	H	H	H	CO_2Me (**1b**)	3	70 (**2b**)	90:10
5	H	H	H	CO_2nBu (**1c**)	3	71 (**2c**)	91:9
6	H	H	H	CO_2tBu (**1d**)	4	71 (**2d**)	93:7
7	H	H	H	CN (**1e**)	3	55 (**2e**)	81:19
8[f]	H	H	H	COMe (**1f**)	5	71 (**2f**)	51:49
9[g]	H	H	H	$P(=O)(OEt)_2$ (**1g**)	3	90 (**2g**)	88:12
10[f]	H	H	Me	CO_2Et (**1h**)	8.6	75 (**2h**)	91:9 (94:6)[h]
11	H	OMe	H	CO_2tBu (**1i**)	10	70 (**2i**)	91:9
12	H	OMe	OMe	CO_2Et (**1j**)	7	63 (**2j**)	89:11 (98:2)[h]
13	OMe	H	OMe	CO_2Me (**1k**)	15	74 (**2k**)	92:8
14[f]	H	$-OCH_2CH_2O-$		CO_2Et (**1l**)	8.5	62 (**2l**)	92:8
15[f]	H	F	H	CO_2Et (**1m**)	9	71 (**2m**)	92:8

[a]Isolated yield. [b]Enantiomeric ratio (er) was determined by chiral HPLC on a Daicel OD-H or IA column. [c]Using cinchonidine (**H**) instead of cinchonine (**G**). [d](*Z*)-Ethyl 3-(2-formylphenyl)acrylate ((*Z*)-**1a**) was used as a substrate. [e]Using **B** instead of **A**. [f]At 25 °C. [g]At 60 °C. [h]After recrystallization.

with natural cinchona alkaloids (**G**−**J**) than their derivatives (**K**−**N**) that are modified at the C9-hydroxy group (entries 2−3 and 9−15). These findings suggest that a free hydroxy group on C9 as a hydrogen bond donor is crucial for the high reactivity of the catalyst. Among NHC precatalysts and cinchona alkaloids, the combination of triazolium salt **A** and cinchonine (**G**) proved to be the most effective catalytic system. Subsequently, we screened other parameters (solvents, temperature, concentration, catalyst loadings, and additives) to find more effective reaction conditions (for details, see the Supporting Information). The lower concentration gave the higher enantiomeric ratio (entry 2 vs entry 3). Lower loading of cinchonine considerably decreased both conversion and enantioselectivity (entry 3 vs entry 16). While our efforts to accelerate the reaction rate by using either additive or additional base were not fruitful, the reaction under high pressure of O_2 while other experimental parameters unaltered resulted in a decreased reaction time with comparable enantioselectivity to the one under air atmosphere (entry 18). Finally, an optimal reaction conditions was established as entry 3 in Table 1, giving **2a** in good yield with high enantiomeric ratio (72%, er 92:8), albeit with long reaction times.

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this process (Table 2). A variety of *α*,*β*-unsaturated esters were more efficient hydrogen bond acceptors than other functionalities in this reaction, thereby generating the corresponding phthalides **2** with good enantiomeric ratios (entries 1−9). However, strong Michael acceptors such as *α*,*β*-unsaturated ketone gave no asymmetric induction even at lower reaction temperature (25 °C, entry 8). Noteworthy is the fact that the (*Z*)-isomer proved to be an

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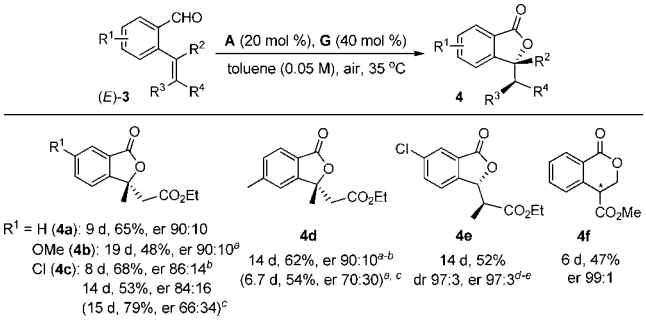
Scheme 2. Asymmetric Oxidative Cyclization Reaction of Di- or Trisubstituted Alkene Derivatives

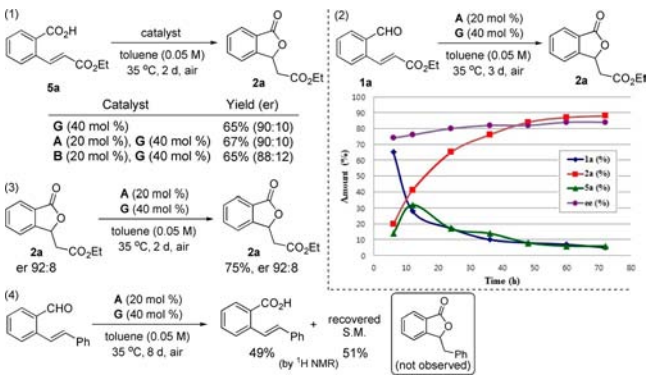


[a]Using **B** instead of **A**. [b]Under O_2 atmosphere (10 atm). [c]From (*Z*)-**3**. [d]At 50 °C. [e]Er of major diastereomer.

unsuitable substrate, leading to **2a** in only moderate yield with lower enantioselectivity (entry 3 vs entry 1). One of the most interesting features of cinchona alkaloids is their availability in two pseudoenantiomeric forms, therefore providing access to both enantiomers of a product.[11] In this context, employing readily available and inexpensive two pseudoenantiomeric forms such as cinchonine (**G**) and cinchonidine (**H**), both (*R*)- and (*S*)-**2a** could be successfully formed with good enantiomeric ratios, respectively (entries 1 and 2).

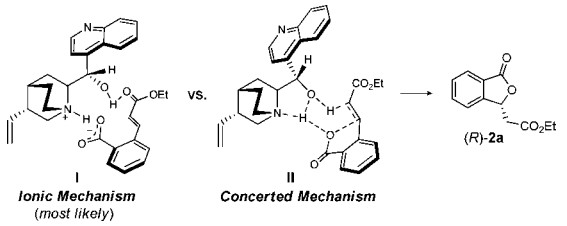
Subsequently, we explored the reaction of trisubstituted alkene substrates (Scheme 2). To our delight, the formation of phthalides **4a**–**d** containing a chiral quaternary carbon center[9] could be achieved in good enantioselectivities. In these cases, similarly to (*Z*)-**1a**, the use of (*Z*)-**3** as a substrate afforded much lower enantioselectivity than that of (*E*)-**3** (e.g., **4c**,**d**). In addition, this protocol could be applied to the highly enantio- and diastereoselective formation of *anti*-**4e**. Next, we proceeded to examine the reaction of α-substituted acrylate **3f** for the formation of 6-membered ring product. Asymmetric protonation[13] occurred successfully, affording **4f** in moderate yields with excellent enantiomeric ratio.

To gain further mechanistic insights into this reaction, a series of control experiments were performed. The reaction of a putative intermediate **5a** either (1) employing only cinchonine (**G**) as a sole catalyst, (2) under our standard reaction conditions, or (3) replacing **A** with **B** under otherwise identical conditions gave similar chemical yield and enantioselectivity of **2a** with a marginal effect of NHC's structure and presence (eq 1). These results support that cinchonine plays a major role in



the stereoselectivity-determining step. Furthermore, in comparison with the outcomes of the reaction of **1a** in Table 1, rather little effect of NHC's structure in the cyclization step of a

Scheme 3



stepwise process indicates that both catalysts exert more influence on each other's function in the one-pot process. The reaction was monitored by ^{1}H NMR, GCMS, and HPLC analyses by withdrawing aliquots at regular intervals over the course of 72 h (eq 2). The putative intermediate **5a** was observed and only moderately increased during the reaction progress. In contrast, product **2a** was forming continuously, while the enantioselectivity of **2a** remained almost constant during the reaction. These findings support that both catalysts are mutually compatible as well as operate concurrently. In addition, subjection of product **2a** to our standard reaction conditions did not result in erosion of product ee (eq 3), suggesting that the product is unlikely to racemize via retro-Michael reaction under these reaction conditions.[14]

Considering the strong influence of C9-OH group on the activity of the catalyst and stereochemical outcome of the reaction, we speculate that the reaction proceeds through dual activation (**I**, Scheme 3). The quinuclidine moiety can deprotonate the $-CO_2H$ group, thus activating it via ion-pair formation for nucleophilic attack on the *Re* face of the alkene, which is activated through hydrogen bonding with the C9-OH group of cinchonine, thus providing preferential formation of (*R*)-**2a**.

On the other hand, an alternative mechanistic mode through transition state **II** can be conceived, which is similar to the one proposed by Hintermann and co-workers.[12a,g] In this mechanism, the hydroxy group of cinchonine takes part in a concerted addition mechanism via *syn* addition, not carbonyl group activation, which is generally accepted since the report of Hiemstra and Wynberg.[11a,12h] In the case of *o*-styryl-substituted benzaldehyde devoid of a hydrogen bond acceptor, no reactivity for cyclization has been observed, leading to the corresponding uncyclized oxidation product (like **5a**) under the standard reaction conditions (eq 4). These findings strongly support both the requirement of hydrogen bond acceptors such as a carbonyl group in the substrate and a bifunctional activation mode involving the tertiary amine base and the hydroxy group. Therefore, while a clear mechanistic picture is elusive at this juncture, we hypothesize that the protocol presented herein seems to follow the Hiemstra–Wynberg model,[11a,12h] an ionic 1,4-addition mechanistic mode via a transition state **I**. In addition, both diastereoselective formation of *anti*-**4e** and asymmetric protonation of **3g** suggest that the ionic 1,4-addition mechanism concludes with an intramolecular proton transfer presumably from the quinuclidine nitrogen to the generated prochiral enolate (*Re* face in the case of **4e**).

In summary, we have developed an asymmetric domino multicatalysis for the synthesis of chiral 3-substituted phthalides. A mutually compatible and cooperative catalyst system by judicious selection of an achiral NHC and a chiral bifunctional catalyst was crucial to the success of this asymmetric domino multicatalysis. Optimum asymmetric induction in this protocol was achieved through noncovalent

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catalysis in a chiral pocket by the use of bifunctional cinchonine catalyst in which tertiary amine (quinuclidine) and hydrogen bond donor (−OH) components simultaneously activate and orient nucleophile and electrophile, respectively. Equally noteworthy is that cinchonine serves as a Brønsted base for NHC generation via deprotonation as well as bifunctional catalyst for asymmetric induction.

Despite a long reaction time and high catalyst loading, this is of great interest since the examples of stereoselective oxa-Michael addition of carboxylic acids[12f] are very rare, although considerable progress has been made in asymmetric oxa-Michael addition of alcohols to α,β-unsaturated carbonyl compounds.[12] Moreover, these new findings may expand the possibilities to develop more effective multicatalysis with the combination of achiral Lewis basic NHC and chiral bifunctional catalyst.[2a,8] Further development of relevant catalytic systems and the elucidation of the mechanism of this reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sowony73@hanyang.ac.kr.

Notes

The authors declare no competing financial interest.

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