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NHC-catalyzed oxidative cyclization reaction for the synthesis of 3-substituted phthalides†

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

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An efficient NHC-catalyzed domino oxidation/oxa-Michael addition reaction of 2-alkenylbenzaldehydes has been developed to afford 3-substituted phthalides bearing a C3-stereogenic center with a broad substrate scope and wide functional group tolerance. The preliminary results of the asymmetric process have been provided as well.

Introduction

Phthalides, in particular those containing a C3-stereogenic center, are versatile building blocks and pervasive motifs in many bioactive natural products (Fig. 1).[1] Consequently, a number of synthetic strategies have been developed for their construction, generally involving the use of chiral auxiliaries and resolutions, chiral organometallics, and transition metal catalysts.[2] However, organocatalytic synthesis of phthalides is very rare in the literature.[3] Wang and Duan demonstrated an aldol-lactonization reaction between 2-formylbenzoates and ketones/aldehydes for the enantioselective synthesis of 3-substituted phthalides using a proline-based secondary amine organocatalyst.[3a] While N-heterocyclic carbenes (NHCs)[4] have rapidly emerged as an important and powerful class of organocatalysts in various synthetic transformations, their uses in the synthesis of phthalides are very limited.[3b,c] Scheidt and Chan showed only a single example, the synthesis of 3-phenylphthalide, as an intramolecular variant in an NHC-catalyzed hydroacylation of activated ketones.[3b] Recently, we reported an NHC-catalyzed oxidative cyclization of 2-alkynylbenzaldehydes under aerobic conditions that enabled the easy preparation of a diverse array of phthalides and isocoumarins (Scheme 1, above).[3c] While it can be a more general method utilizing NHCs as organocatalysts for the synthesis of 3-substituted phthalides, inseparable mixtures of two isomers, phthalides and isocoumarins, were obtained in most cases and, most of all, there is no stereogenic center at the C3 position of 3-substituted phthalides due to it being an sp^2-carbon. In view of the biological importance of the chiral 3-substituted phthalides, various benefits of organocatalysis as an attractive alternative to metal catalysis,[5] and the potential of application in enantioselective oxidative NHC organocatalysis,[4b,c] we were interested in developing a new, efficient method catalyzed by NHC for the facile construction of a 3-substituted phthalide motif bearing a C3-stereogenic center. In light of our recent success in the NHC-catalyzed oxidative cyclization of 2-alkynyl-

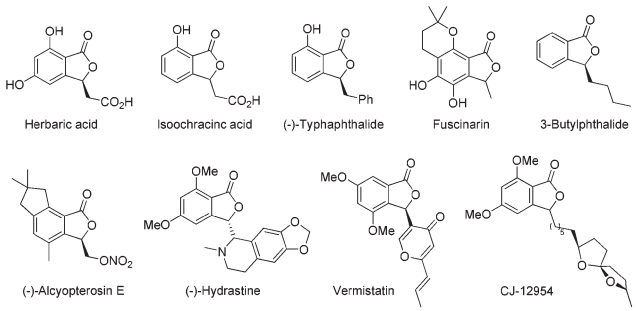
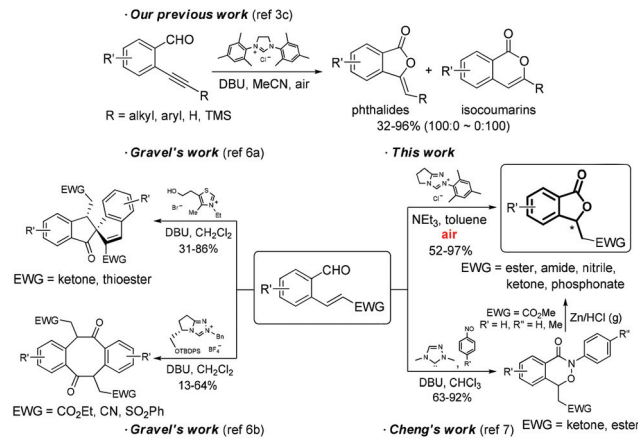


Fig. 1 Selected examples of naturally occurring 3-substituted phthalide derivatives.



Scheme 1

Department of Chemistry and Research Institute for Natural Sciences, Hanyang University, Seoul 133-791, Korea. E-mail: sowony73@hanyang.ac.kr

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benzaldehydes,[3c] we naturally envisaged the use of 2-alkenylbenzaldehydes as a substrate for such a reaction (Scheme 1).

On the other hand, NHC-catalyzed reactions of 2-alkenylbenzaldehydes under an inert atmosphere were reported to provide either spiro bis-indanes or dibenzo[8]annulenes *via* a domino Stetter–aldol-Michael or double Stetter reaction, respectively.[6] Furthermore, in another example using the same substrates under NHC catalysis, a domino aza-benzoin/intramolecular oxa-Michael addition reaction was carried out with nitrosoarenes to afford 2,3-benzoxazin-4-ones, which could be further transformed into a phthalide (R′ = H, EWG = CO_2Me).[7] Given the biological importance of the 3-substituted phthalides and the ever increasing necessity of new atom- and step-economical, sustainable, and eco-friendly methods for the synthesis of valuable compounds, an expedient and efficient synthetic protocol under atmospheric oxygen can lead to a facile and desirable route to the intriguing phthalide motif.

Herein we disclose the realization of this proposal. It is worthy of note that this process shows a broad substrate scope and wide functional group tolerance. An oxidation–cyclization sequence involving a 2-alkenylbenzoic acid intermediate was proposed and the preliminary results of the asymmetric process have been provided.

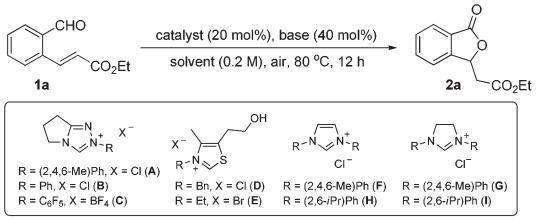
Results and discussion

We began our studies on the proposed reaction using **1a** as the test substrate and examined the reaction parameters to identify the optimal conditions (Table 1). In contrast to our previous work,[3c] the combination of triazolium salt **A** and NEt_3 or DMAP in toluene proved to be superior for this reaction, among a variety of heterazolium salts, bases, and solvents examined. Finally, the optimal result was obtained in the presence of 20 mol% **A** and 40 mol% NEt_3 in toluene (0.2 M) at 80 °C, providing **2a** in 96% yield (by ^{1}H NMR).

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this process. A variety of electron-withdrawing substituents at the alkene moiety were well tolerated in this reaction, thereby generating the corresponding phthalides **2** in moderate to good yields (Table 2, entries 1–11). α,β-Unsaturated ketones displayed a higher reactivity than others, requiring a lower reaction temperature (25–60 °C, Table 2, entries 8–10). It is worth noting that the (*Z*)-isomer (**1a′**) required more forcing conditions for the reaction to take place and led to **2a** in only moderate yield even at elevated temperature (100 °C, Table 2, entry 2). Next, we proceeded to examine the effect of substituents on the aromatic ring of 2-alkenylbenzaldehydes (Table 2, entries 12–19). The yields remained equally good with both electron-donating and -withdrawing substituents on the aromatic ring. Electron-donating and -withdrawing substituents *para* to the alkene moiety (R^2) had no significant effect on the reactivity. However, the *ortho* substituents (R^1) and electron-donating substituents *para* to the aldehyde moiety (R^3) appeared to retard the reaction considerably, presumably as a consequence of steric hindrance and the reduced electrophilicity of the aldehyde carbon toward reaction with the NHC catalyst, respectively (Table 2, entries 15–17). Equally noteworthy is that this process can tolerate a variety of functional groups including methoxy, halogen, ester, amide, nitrile, ketone, and phosphonate moieties.

Subsequently, we explored the reaction of trisubstituted alkene substrates. To our delight, the oxidative cyclization reactions of **3** also proceeded successfully, to afford the corresponding phthalides in moderate to good yields (Table 3), although they generally required more forcing conditions (higher reaction temperature or higher pressure of O_2) and/or longer reaction times for satisfactory conversion, presumably due to the steric and electronic effects. In addition, aryl-substituted alkene substrates (**1s–t**) afforded the related uncyclized products (**5s–t**) as the sole or major product, and attempts to induce further cyclization were unsuccessful (eqn (1)). These findings imply that 2-alkenylbenzoic acids could be generated from an NHC-catalyzed preoxidation of 2-alkenylbenzaldehydes under aerobic conditions, which could be a plausible

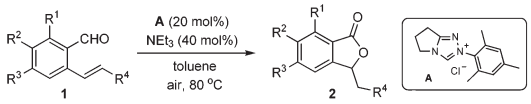
Table 1 Optimization studies



Entry	Catalyst	Base	Solvent	Yield[a] (%)
1	**A**	DBU	Toluene	60
2	**B** or **C**	DBU	Toluene	34–38
3	**D** or **E**	DBU	Toluene	16–17
4	**F**	DBU	Toluene	36
5	**G**	DBU	Toluene	55
6	**H** or **I**	DBU	Toluene	24–26
7	**A**	**NEt_3 or DMAP**	**Toluene**	**96–100**
8	**A**	iPr_2NEt	Toluene	84
9	**A**	NaOAc or KHMDS	Toluene	71–73
10	**A**	Na_2CO_3, K_2CO_3, Cs_2CO_3, KOH, or K_3PO_4	Toluene	26–61
11	**A**	NaH or *t*BuOK	Toluene	20–34
12	**A**	NEt_3	MeCN, dioxane, or DMF	66–79
13	**A**	NEt_3	*t*BuOH, DMSO, or DCE	41–53
14	**A**	NEt_3	THF, acetone, or EtOH	13–28
15[b]	**A**	NEt_3	Toluene	80–85
16[c]	**A**	NEt_3	Toluene	72
17[d]	**A**	NEt_3	Toluene	89

[a] Yields were determined by ^{1}H NMR using trichloroethylene as an internal standard. [b] At 60 °C under either air or O_2 (1 atm). [c] With 10 mol% **A** and 20 mol% NEt_3 for 22 h. [d] In toluene (0.1 M).

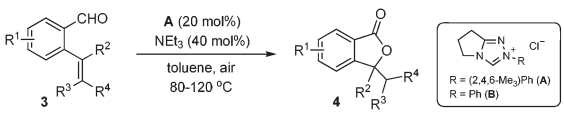
Table 2 NHC-catalyzed oxidative cyclization reaction of 2-alkenylbenzaldehydes

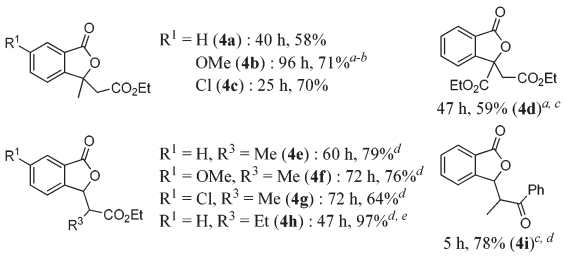


Entry	R^1	R^2	R^3	R^4	Time (h)	Yield[a] (%)
1	H	H	H	CO_2Et (**1a**)	12	86 (**2a**)
2[b,c]	H	H	H	CO_2Et (**1a′**)	9	47 (**2a**)
3	H	H	H	CO_2Me (**1b**)	24	90 (**2b**)
4	H	H	H	CO_2nBu (**1c**)	24	88 (**2c**)
5	H	H	H	CO_2tBu (**1d**)	8	64 (**2d**)
6	H	H	H	$CONMe_2$ (**1e**)	24	80 (**2e**)
7	H	H	H	CN (**1f**)	22	72 (**2f**)
8[d]	H	H	H	COMe (**1g**)	24	79 (**2g**)
9[d]	H	H	H	COEt (**1h**)	24	72 (**2h**)
10[e]	H	H	H	COPh (**1i**)	10	52 (**2i**)
11[c]	H	H	H	$P(=O)(OEt)_2$ (**1j**)	48	84 (**2j**)
12	H	H	Me	CO_2Et (**1k**)	7	79 (**2k**)
13	H	OMe	H	CO_2Et (**1l**)	6	77 (**2l**)
14	H	OMe	H	CO_2tBu (**1m**)	72	92 (**2m**)
15	H	OMe	OMe	CO_2Et (**1n**)	51	82 (**2n**)
16[c]	OMe	H	OMe	CO_2Me (**1o**)	48	86 (**2o**)
17	H	$-OCH_2CH_2O-$		CO_2Et (**1p**)	24	80 (**2p**)
18	H	Cl	H	CO_2Et (**1q**)	6	69 (**2q**)
19	H	F	H	CO_2Et (**1r**)	7	65 (**2r**)

Reaction conditions: **1** (1 equiv.), **A** (20 mol%), and NEt_3 (40 mol%) in toluene (0.2 M) at 80 °C under aerobic conditions, unless otherwise noted. [a] Isolated yield. [b] (*Z*)-Ethyl 3-(2-formylphenyl)acrylate (**1a′**) was used as a substrate. [c] At 100 °C. [d] At 60 °C. [e] At 25 °C.

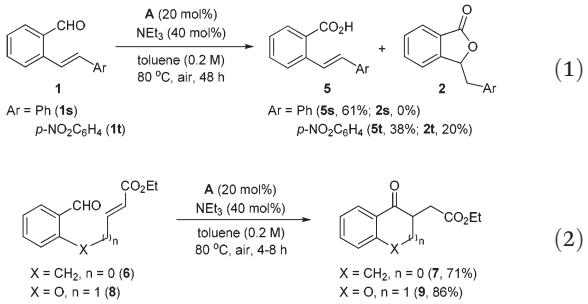
Table 3 NHC-catalyzed oxidative cyclization reaction for the synthesis of various phthalides





Reaction conditions: **3** (1 equiv.), **A** (20 mol%), and NEt_3 (40 mol%) in toluene (0.2 M) at 100 °C under aerobic conditions, unless otherwise noted. Isolated yields are given. [a]Using **B** instead of **A**. [b]At 120 °C. [c]At 80 °C. [d]Diastereomeric ratios (dr) = ~1 : 1. [e]Under O_2 atmosphere (10 atm).

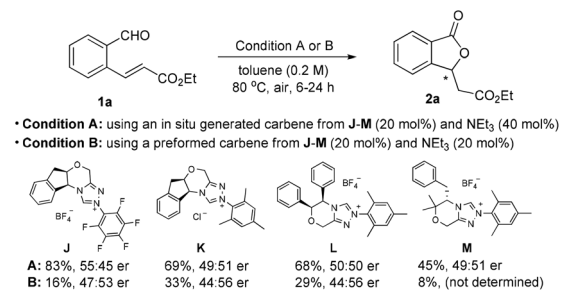
intermediate in this oxidative cyclization reaction, in close analogy to our previous report.[3c,4b,c,8] Furthermore, these results also indicate a requirement for the alkene to be substituted with carbonyl or related electron-withdrawing functional groups, having heteroatoms with lone pair electrons, in order for the subsequent cyclization reaction to take place. Carbonyl groups can be coordinated by the conjugate acid of the base, leading to a more electrophilic alkene moiety. In this regard, a conjugate acid could be generated from the deprotonation process, either between excess NEt_3 and the $-CO_2H$ group of the speculated intermediate (Scheme 3a) or between triazolium salt **A** and NEt_3 for the preparation of an NHC species[9] (Scheme 3b) (*vide infra*).



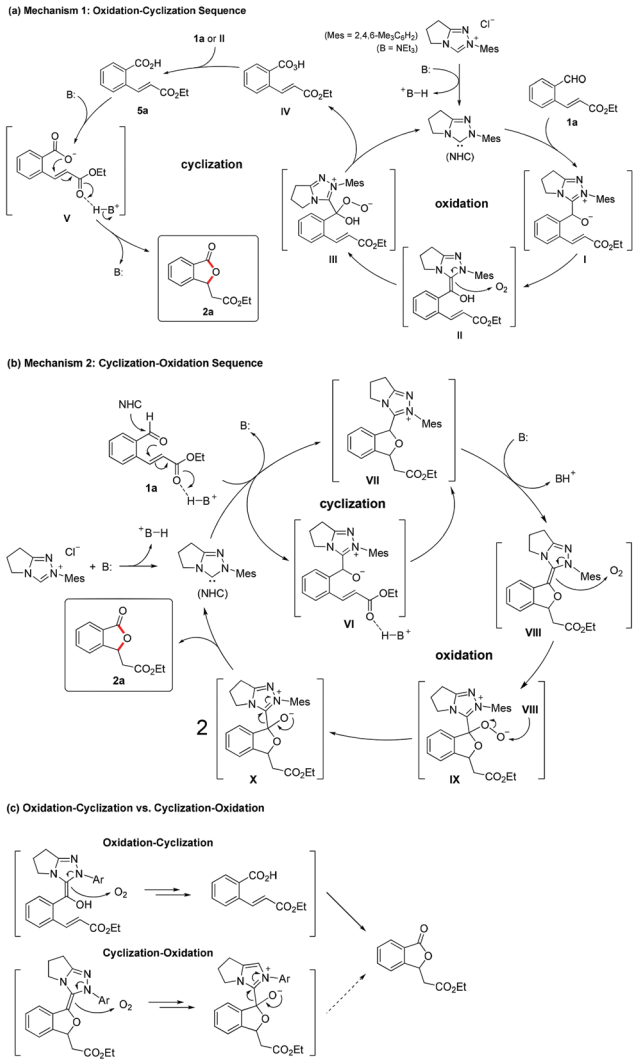
Next, we proceeded to the application of this reaction system to the formation of 6- and 7-membered ring products using **6** and **8**, respectively (eqn (2)). Instead of the expected lactone derivatives, however, indanone **7** and chromanone **9** were obtained exclusively *via* the Stetter reaction.[4,10]

Encouraged by the successful synthesis of various 3-substituted phthalides, we turned our attention to the enantioselective version of this oxidative cyclization reaction, which would be highly useful and sought after. We examined various chiral triazolium salts and reaction parameters for the asymmetric reaction of **1a** (Scheme 2). Very disappointingly, however, no or only modest stereoselectivities were obtained. The low reactivity of the reactions using a preformed carbene in the absence of additional base (condition B) indicates the requirement for an excess amount of base for efficiency of the reaction.

Based on our findings, and by analogy with the mechanism proposed for the related NHC-catalyzed reactions under aerobic conditions,[3c,4b,c,8,11] two plausible mechanisms for this oxidative cyclization reaction can be conceived as follows (Scheme 3): (1) oxidation–cyclization and (2) cyclization–oxidation sequence. In the oxidation–cyclization sequence, the



Scheme 2 Preliminary results on NHC-catalyzed asymmetric oxidative cyclization reaction.



Scheme 3 Proposed mechanism.

Breslow intermediate **II**, formed by an initial nucleophilic addition of an *in situ* generated NHC species to the aldehyde functional group, is incorporated with electrophilic O_2, followed by the intramolecular oxa-Michael reactions of the resulting 2-alkenylbenzoic acid intermediate **5a** (Scheme 3a). Alternatively, a cyclization–oxidation mechanism involving the intramolecular cyclization of 2-alkenylbenzaldehydes through a concerted or stepwise pathway prior to oxidation with O_2 could also be proposed (Scheme 3b).[11a,12] In the latter case, wherein NHC is incorporated in the cyclization step, better asymmetric induction by chiral NHCs could be expected compared to our results shown in Scheme 2. Furthermore, observation of both no lactone formation in the reaction of **6** and **8** (eqn (2)) and very low reactivity in the absence of excess base (condition B in Scheme 2) is contrary to a cyclization–oxidation pathway. The former results suggest that the Stetter reaction of **6** and **8** *via* a **II**-type intermediate is much faster than the aldehyde oxidation reaction. In stark contrast, unfavorable 4-membered ring formation with significant ring strain seemingly prevented **1** and **3** from the Stetter reaction.[13] Instead, oxidation preferentially precedes the cyclization reaction, resulting in 5-membered ring formation.

Therefore, although a mechanism remains elusive at this juncture, the oxidation–cyclization pathway seems to work in this protocol, promoting the sequential oxidation/oxa-Michael addition reaction and involving 2-alkenylbenzoic acid intermediates (Scheme 3c). In addition, in a series of detailed ^{1}H NMR analyses during the reaction progress, the putative intermediate **5a** (and possibly other species such as **II** or **III**) could be observed (for details, see ESI†). In the cases of the reactions under condition B in Scheme 2, deprotonation of intermediate **5a** could be achieved by a chiral NHC (*i.e.*, B: = NHC in the cyclization catalytic cycle in Scheme 3a),[9a,14] whose conjugate acid coordinates to a carbonyl oxygen atom for the subsequent cyclization reaction to take place. No stereoinduction and low reactivity under these conditions suggest that a tighter chiral pocket and excess base would be needed for better stereocontrol and reactivity, respectively.

Conclusions

In summary, we have developed an efficient NHC-catalyzed domino oxidation/oxa-Michael addition reaction of 2-alkenylbenzaldehydes. This protocol represents an atom/step economical, sustainable, and eco-friendly route for the facile construction of biologically important 3-substituted phthalides bearing a C3-stereogenic center. Equally noteworthy is that this process can tolerate a variety of functional groups.

The success of this sequential process could be achieved both by exploiting atmospheric oxygen as an oxygen atom source and by introducing an electron-deficient alkene moiety bearing heteroatoms with lone pair electrons, activated by the *in situ* generated conjugate acid of the base. It is worth noting that molecular oxygen in air plays an essential role as the source of the "O" atom in this transformation, and the reaction atmosphere has a pronounced effect on the reaction outcomes since, as mentioned earlier, the similar NHC-catalyzed reactions of the same substrates under an inert atmosphere afforded very different products through different reaction pathways (Scheme 1).[6]

Mechanistically, this protocol might follow the oxidation–cyclization sequence, involving 2-alkenylbenzoic acid intermediates. In addition, the preliminary results of our investigations into an enantioselective NHC-catalyzed oxidative cyclization reaction demonstrate that both a tight chiral pocket and excess base may be required for good stereocontrol and reactivity, respectively. These new findings may present new ideas and possibilities to develop an effective multicatalysis with the combination of NHC and a chiral co-catalyst. Further investigations along this direction will be reported in due course.

Experimental

General procedure for the NHC-catalyzed oxidative cyclization reactions of 2-alkenylbenzaldehydes

To a solution of the substrate **1**, **3**, **6**, or **8** (0.100 mmol, 1 equiv.) in toluene (0.5 mL, 0.2 M) was added 2-mesityl-2,5,6,7-tetrahydropyrrolo[2,1-*c*][1,2,4]triazol-4-ium chloride (**A**) (5.4 mg, 0.020 mmol, 20 mol%) and NEt_3 (6 μL, 0.040 mmol, 40 mol%). The resulting mixture was stirred at the reported temperature for the reported time under aerobic conditions. After the reaction was completed, the reaction mixture was cooled to room temperature, diluted with distilled water, extracted with CH_2Cl_2 (three times), dried over $MgSO_4$, and concentrate *in vacuo*. The residue was purified by column chromatography on silica gel to give the corresponding product.

Acknowledgements

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