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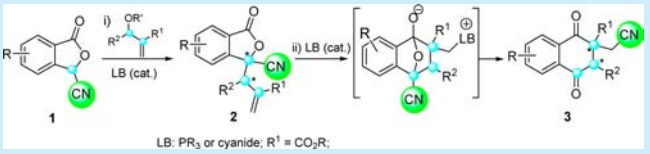
Asymmetric Synthesis of Functionalized Dihydronaphthoquinones Containing Quaternary Carbon Centers via a Metal-Free Catalytic Intramolecular Acylcyanation of Activated Alkenes

Zhe Zhuang, Zhi-Peng Hu, and Wei-Wei Liao*

Department of Organic Chemistry, College of Chemistry, Jilin University, 2699 Qianjin Street, Changchun 130012, China

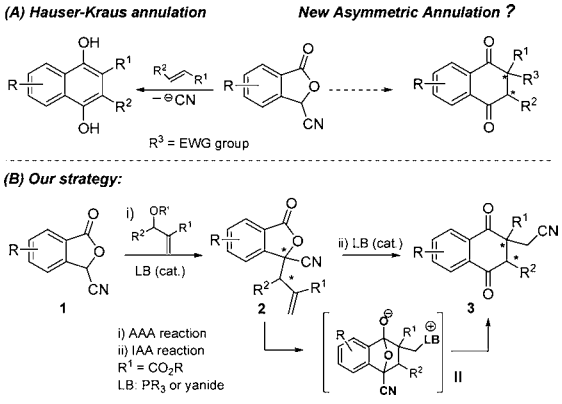
Supporting Information

ABSTRACT: A novel metal-free catalytic annulation was developed through a Lewis base-catalyzed asymmetric allylic alkylation and the ensuing unprecedented asymmetric intramolecular acylcyanation of alkenes. This protocol provides a unique and facile access to prepare enantioenriched densely functionalized dihydronaphthoquinones accompanied by enantiomerically pure 3,3-disubstituted phthalides bearing quaternary carbon centers.



To develop new enantioselective transformations to meet an increasing demand for the economical syntheses of enantiomerically pure chiral compounds is a great continuous challenge for synthetic chemists.[1] Among them, asymmetric annulations have proven to be efficient synthetic routes to access chiral compounds.[2] The Hauser−Kraus annulation reported in 1978 has found wide applications in assembling many important naphthol/naphthoquinone based frameworks in synthetic chemistry (Scheme 1A).[3] In a typical Hauser−Kraus annulation,

Scheme 1. Synthetic Strategies



3-cyanophthalide is utilized as an annulating agent to react with various activated alkenes to construct highly substituted 1, 4-dioxygenated naphthalenes, and the entire process involves fusion of a new ring to a molecule via two new bonds and the expulsion of stoichiometric cyanide ion as waste. However, the distinct feature of this classic transformation wherein all generated sp^3 carbon centers undergo further aromatization to offer a substituted aromatic ring impedes the potential generation of chiral sp^3 carbon centers and makes the application of this annulation strategy to an asymmetric C−C bond formation reaction inconceivable.

Recently, we reported the first metal-free intramolecular carbocyanations of alkenes which provided an efficient approach to construct nitriles with diverse carbon frameworks incorporating quaternary carbon centers.[4,5] Inspired by the high efficiency of Hauser−Kraus annulation on C−C bond formation and recent reports from our laboratory, we hypothesize that a novel atom-economic asymmetric annulation which would take full advantages of the elements of Hauser−Kraus annulation and the principle of metal-free intramolecular acylcyanations of alkenes (IAA) can be established and would construct enantioenriched and carboannulated functionalized dihydronaphthoquinone structural motif incorporating a cyano group in catalytic fashion as follows: a metal-free catalytically generated enantiomerically enriched 3-allylic-3-cyano-substituted phthalide **2**, formed via a Lewis base-catalyzed asymmetric allylic alkylation (AAA),[6] would undergo a Lewis base mediated acylcyanation of activated alkenes to furnish annulated enantioenriched dihydronaphthoquinone **3** enantiospecifically via a putative highly functionalized intermediate (**II**) (Scheme 1B). This novel protocol would be highly attractive not because it offers a unique strategy to design and develop new asymmetric annulation methods to access a diverse pool of enantioenriched densely functionalized dihydronaphthoquinones accompanied by enantiomerically pure 3,3-disubstituted phthalides bearing quaternary carbon centers[7,8] but also greatly extends the applicability of metal-free intramolecular carbocyanations of alkenes on assembling enantiopure substrates containing higher levels of molecular complexity in possession of cyclic frameworks in contrast to our previous works. Herein, we report our results of this unprecedented annulation via a metal-free AAA and the ensuing IAA reactions.

Given that practical access to enantioenriched 3-allylic-3-cyano substituted phthalides would be crucial to investigate this unique annulation, we first assessed the feasibility of enantioselective construction of these chiral scaffolds via a

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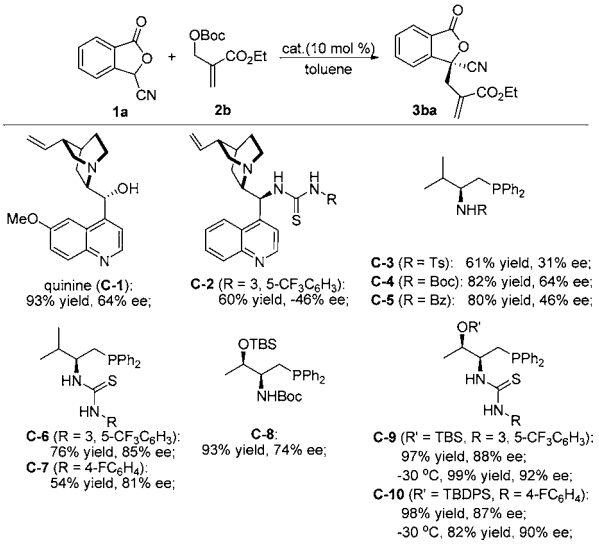
Lewis base-catalyzed AAA reaction. Although AAA reactions of 3-carboxylate phthalides with the substituted Morita–Baylis–Hillman (MBH) carbonates have been reported,[6h] the employment of 3-cyano phthalides in this allylic alkylation has not been developed. Besides, the enantioselective examples of pronucleophiles with the unsubstituted MBH carbonates in this alkylation are rare. Keeping these surveys in mind, our initial efforts focused on the identification of effective catalysts and conditions for the enantioselective allylic alkylation reaction between 3-cyanophthalide **1a** and unsubstituted MBH carbonate **2b** to afford 3,3-disubstituted phthalide **3ba** (Scheme 2). Cinchona alkaloid

Scheme 2. Selection of Chiral Catalysts Examined

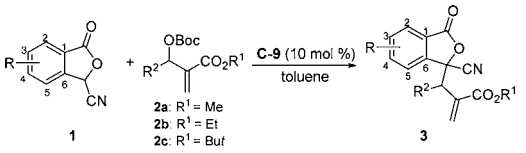


derivatives were selected as catalysts first and provided the moderate enantioselectivity. To our delight, bifunctional phosphines incorporating thioureas moieties and hindered silyloxy groups were found to be superior in stereochemical control, which furnished the desired product **3ba** in high yields with 87% and 88% ee, respectively, by using catalyst **C-9** and **C-10**. Decreasing the reaction temperature resulted in the best stereochemical control and excellent chemical yield in the presence of catalyst **C-9** (99% yield, 92% ee).

We next examined the substrate scope of phosphine (**C-9**)-catalyzed enantioselective allylic alkylation reactions of MBH carbonates **2** with 3-cyanophthalides **1** (Table 1). In general, high yields and enantioselectivities were observed for a broad range of phthalides. 3-Allylic-3-cyano-substituted phthalides, having electron-deficient groups at the 4-position gave excellent results (Table 1, entries 8–10), while 3-fluoro-substituted phthalide provided the decreased enantioselectivity (Table 1, entry 11). The more electron-rich group substituted phthalides generally required higher reaction temperatures and gave high enantioselection (Table 1, entries 3–7). The reaction between **1a** and MBH carbonates **2c** with bulky ester groups afforded the product **3ca** in high yield with the decreased ee value, while treatment of **1a** and MBH carbonate **2a** provided chemical and optical yields similar to those of its ethyl ester analogue **2b** (Table 1, entries 12 and 13). MBH carbonates with the alkyl moieties were well-tolerated and delivered the congested products **3** in good to high yields and excellent enantioselectivities (up to 99% ee, Table 1, entries 14 and 15), albeit with low diastereoselectivity.[9]

With these enantioenriched 3,3-disubstituted phthalides in hand, we set out to study this novel annulation via metal-free IAA

Table 1. Screening of AAA Reactions[a]

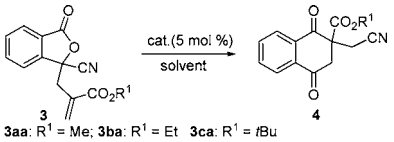


entry	R	R^2	2	time (h)	yield[b] (%)	ee[c] (%)
1	H	H	**2b**	24	99 (**3ba**)	92
2	4-Me	H	**2b**	36	92 (**3bb**)	88
3[d]	4-OMe	H	**2b**	1	99 (**3bc**)	89
4[d]	3-Me	H	**2b**	1	92 (**3bd**)	93
5[d]	2-OMe	H	**2b**	1	91 (**3be**)	90
6[d]	3,4-Me	H	**2b**	1	97 (**3bf**)	95
7[d]	4,5-OMe	H	**2b**	1	99 (**3bg**)	92
8	4-F	H	**2b**	24	99 (**3bh**)	96
9	4-Cl	H	**2b**	24	99 (**3bi**)	96
10	4-Br	H	**2b**	24	99 (**3bj**)	96
11	3-F	H	**2b**	24	73 (**3bk**)	82
12	H	H	**2a**	48	98 (**3aa**)	90
13	H	H	**2c**	48	97 (**3ca**)	81
14	H	Me	**2d**	48	94 (**3da**)	99[e,f]
15[d]	H	*n*Pr	**2e**	24	73 (**3ea**)	96[e,g]

[a]Performed with **1** (0.1 mmol), **2a** (0.12 mmol), and catalyst **C-9** (10 mol %) in toluene (1.0 mL) at −30 °C. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Performed with 4 Å MS at 25 °C. [e]Ee value of major diastereomer; dr value was determined by ^{1}H NMR analysis. [f]dr = 2.5/1. [g]dr = 2.3/1.

reaction (Table 2). The intramolecular acylcyanation of compound **3ba** was investigated first in DMSO with a catalytic

Table 2. Optimization of Annulation Reactions[a]



entry	cat.	3	solvent	time (h)	yield[b] (%)	es[c] (%)
1	TBACN	**3ba**	DMSO	1	70 (**4ba**)	85
2	PBu_3	**3ba**	DMSO	24	29 (**4ba**)	89
3	$PPhEt_2$	**3ba**	DMSO	24	39 (**4ba**)	86
4	PPh_3	**3ba**	DMSO	12	*d*	
5	TBACN	**3ba**	DMF	12	69 (**4ba**)	88
6	TBACN	**3ba**	HMPA	12	*d*	
7	TBACN	**3ba**	NMP	24	68 (**4ba**)	90
8	TBACN	**3aa**	NMP	24	59 (**4aa**)	86
9	TBACN	**3ca**	NMP	24	52 (**4ca**)	86
10[e]	TBACN	**3ba**	NMP	48	57 (**4ba**)	94
11[e]	TBACN	**3ba**	NMP	72	71 (**4ba**)	95
12[e,f]	TBACN	**3ba**	NMP	48	72 (**4ba**)	86

[a]Performed with **3ba** (0.1 mmol) and catalyst (5 mol %) in solvent (1.0 mL) at 25 °C. [b]Isolated yields. [c]es = (product ee/starting material ee) × 100%. Ee values were determined by chiral HPLC analysis. [d]No desired product was detected. [e]Run at 0 °C. [f]TBACN (10 mol %) was used.

amount of TBACN (tetrabutylammonium cyanide), which was previously identified as effective catalyst in intramolecular carbocyanation of cyanohydrins and α-amino nitriles.[4,10] To our delight, the desired annulation occurred and gave rise to the highly functionalized dihydronaphthoquinone product **4ba** in

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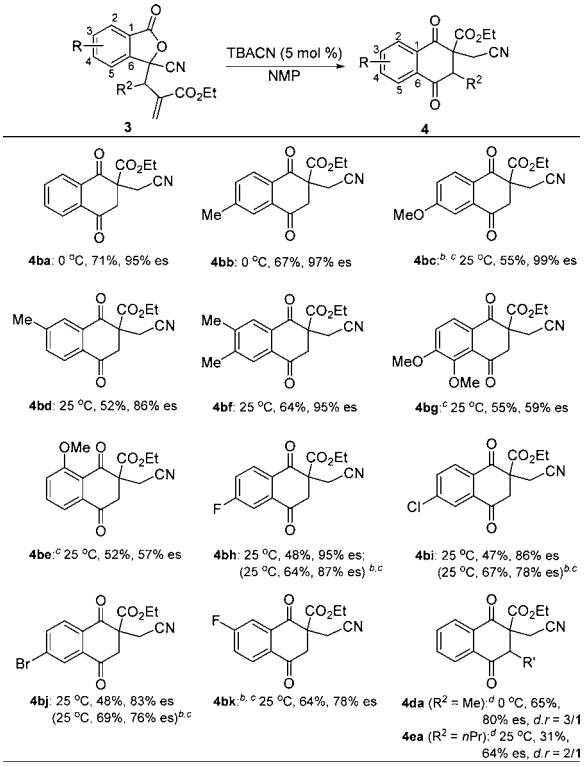
70% yield in the presence of TBACN (5 mol %) with good chirality transfer (85% es, Table 2, entry 1). Phosphine catalysts such as $PPhEt_2$ and PBu_3 (5 mol %) gave the lower conversion with the marginally high stereospecificities, whereas the reaction did not occur in the presence of PPh_3 (Table 2, entries 2−4). Further survey on solvents revealed that the acylcyanation reaction worked well in polar solvents in the presence of catalytic amount of TBACN, with regard to the chemical yield and efficiency of chirality transfer.[11] The higher es value was observed in DMF, while chemical yield was similar to that of DMSO (Table 2, entry 5). However, nondesired product was detected in HMPA (Table 2, entry 6). The further enhanced es value was obtained in NMP which provided **4ba** in 68% yield with 90% es (Table 2, entry 7). Methyl and *tert*-butyl ester analogues (**3aa** and **3ca**) were employed, and both yield and es value decreased marginally (Table 2, entries 8 and 9). Decreasing temperature improved the efficiency of chirality transfer markedly (95% es and 71% yield), albeit with prolonged reaction time (Table 2, entries 10 and 11). The attempt to accelerate this process by increasing the amount of TBACN worked, whereas the effectiveness of chirality transfer deteriorated dramatically (Table 1, entry 12).

With the optimal reaction condition established, the substrate scope of metal-free catalyzed asymmetric annulation was examined (Scheme 3). Phthalides including electron-donating groups at the 4-substituted provided the desired products in good yields with excellent es value (**4bb**−**bc**), while substrates possessing electron-withdrawing groups at the 4-position furnished functionalized dihydronaphthoquinones in similar yields with decreased es value (**4bi**−**bj**), except for 4-fluoro-substituted phthalide which delivered the high stereospecificity (**4bh**). These results indicated that the chirality transfer rather relied upon the electronic properties of the aromatic system of 3,3-disubstituted phthalides **3** in developed process. The reactions of phthalides containing substituents at the 3-postion worked well and provided the desired products in moderate yields and with the lower stereospecificities than that of the corresponding 4-substituted phthalides (**4bd** and **4bk**). 3,4-Dimethyl-substituted phthalide can also serve as suitable substrate to give the desired product with the similar chemical yield and stereospecificity to that of the 4-position substituted analogue (**4bf**). In contrast, the asymmetric annulations of phthalides with substituents at the 2 or 5 position demonstrated the different stereospecificities. The intramolecular acylcyanation of 2-methoxy-substituted phthalide gave the desired product with moderate es value (**4be**), while the 5-substituted analogue provided the worst stereospecificity and 4,5-dimethoxy-substituted phthalide gave the similar results to that of the 2-substituted analogue (**4bg**),[12] which is in accord with the proposed mechanism, in which a 2- or 5-substitution pattern would result in an unstable intermediate **II** (Scheme 1) due to the unfavorable steric interaction between the 2- (or 5-) substituted group and oxyanion (or cyano group).[13] Furthermore, enantioenriched phthalides bearing adjacent quaternary and tertiary stereogenic centers have been examined. Treatment of phthalide **3da** furnished the corresponding product **4da** incorporating adjacent quaternary and tertiary stereogenic centers in 65% yield with 80% es, while *n*-propyl-substituted **3ea** gave the desired product **4ea** in relatively low yield with moderate es value.

The absolute configurations of the newly formed quaternary centers of both enantioenriched 3,3-disubstituted phthalide **3bj** and the corresponding dihydronaphthoquinone drivative were determined on the basis of X-ray crystal structural analyses (see the Supporting Information for details). Based on the observed stereochemistry, a possible reaction mechanism is depicted in Scheme 4. In accord with the previous proposed mechanism, an enolate was first generated from the Michael addition of cyanide ion to activated C═C bond of enantioenriched 3,3-disubstituted phthalide **3** in this annulation. Due to the facial selectivity of enolate (**I-A**), subsequently a tandem intramolecular condensation between the enolate (*Si* face) with the ester group pro ceeded stereospecifically and gave intermediate **II-A**, which followed an elimination to afford the desired product **4**-(*R*) with cyanide ion.

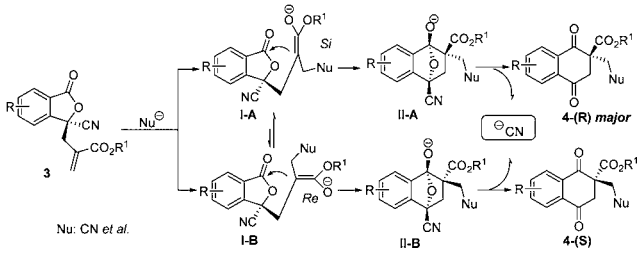
It is noteworthy that this novel annulation protocol can be further extended beyond the metal-free intramolecular acylcyanation. For example, nucleophiles such as alkyl anion also can be employed in this annulation and react with **3ba** to provide functionalized dihydronaphthoquinone **4bl** in 67% yield with

Scheme 3. Substrate Scope of Annulation Reactions[a]



[a]Performed with **3** (0.1 mmol) and TBACN (5 mol %) in NMP. Yields shown are of isolated products. For details, see the Supporting Information. [b]TBACN (10 mol %). [c]Run in DMSO. [d]Run in DCM with TBACN (10 mol %).

Scheme 4. Proposed Mechanism



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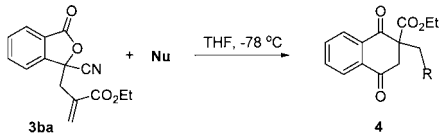
good es value, which further expanded the applicability of this synthetic strategy remarkably (Scheme 5).

Scheme 5. Extention of Annulation



In summary, we have developed an unprecedented catalytic intramolecular annulation via a metal-free AAA and the ensuing IAA reactions which provided a unique and facile access to prepare enantioenriched densely functionalized dihydronaphthoquinones accompanied by enantiomerically pure 3,3-disubstituted phthalides bearing quaternary carbon centers under neutral and mild conditions. The scope and versatility of the process was demonstrated. Further extension of this synthetic strategy also has been exhibited. Efforts on the studies of the synthetic applications are ongoing in our laboratories.

■ 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: wliao@jlu.edu.cn.

Notes

The authors declare no competing financial interest.

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(11) See the Supporting Information for details.

(12) The annulation of 5-methoxy-substituted phthalide (93% ee) gave the desired product in almost racemic form under the same reaction conditions as that of **3be**.

(13) The unfavorable steric interaction between the 2- (or 5-) substituted group and oxyanion (or cyano-group) in a 2- or 5-substitution pattern may result in the possibly reversible equilibrium between intermediate **I** and **II** (Schem 4) and subsequently bring a rapid equilibrium between **I-A** and **I-B**, which may lead to the racemization of the annulation of 2- or 5-substituted phthalide.