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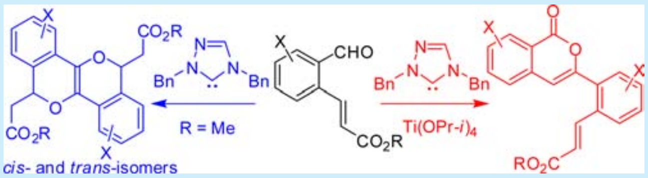
Changing Reaction Pathways of the Dimerization of 2-Formylcinnamates by N-Heterocyclic Carbene/Lewis Acid Cooperative Catalysis: An Unusual Cleavage of the Carbon−Carbon Bond

Hai-Yan Dang,† Zi-Tian Wang,† and Ying Cheng*

College of Chemistry, Beijing Normal University, Beijing 100875, China

Supporting Information

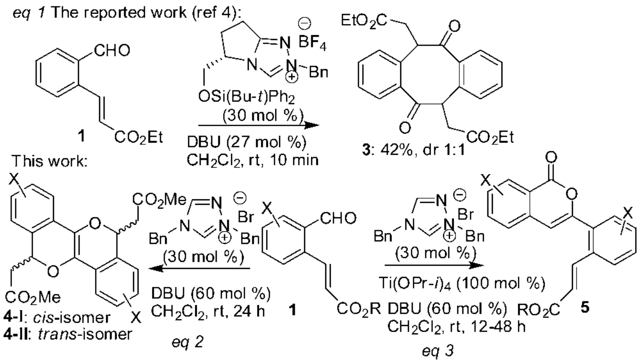
ABSTRACT: Catalyzed by a triazole carbene, the dimerization of 2-formylcinnamates underwent benzoin condensation followed by intramolecular oxa-Michael addition to afford isochromeno[4,3-*c*]isochromene products. Under the catalysis of a combination of triazole carbene and Ti(OPr-*i*)$_4$ catalysts, the dimerization reaction of 2-formylcinnamates proceeded through a completely different route to furnish the formation of isochromenone derivatives with the elimination of an acetate moiety.



N-Heterocyclic carbene (NHC) catalysis has been developed in the past decades into a powerful strategy for carbon−carbon and carbon−heteroatom bond-forming reactions.[1] Very recently, a few dual catalytic approaches using NHCs in combination with a Lewis acid show unique advantages and are attracting great interest.[2] The cooperative catalysis of NHCs and Lewis acids has been demonstrated to enhance the reactivity of substrates, to improve stereoselectivity, and to reverse facial selectivity or regioselectivity.[3] For example, the chemical yield of [3 + 2] annulation product from the reaction of an α,β-unsaturated aldehyde with a hydrazone was significantly improved from 31% to 78% by using the combined catalysts of a triazole carbene and Mg(OBu-*t*)$_2$.[3a] While alkynyl aldehydes did not react with isatins or unsaturated α-ketoesters in the presence of either a triazole or an imidazoline carbene, these substrates reacted to produce [3 + 2] annulation products in good yields under the cooperative catalysis of both carbene and LiCl.[3b,c] Similarly, whereas no reaction took place between α,β-unsaturated aldehydes and β,γ-unsaturated α-ketoesters in the presence of an imidazole or a chiral triazole carbene, cyclopentane derivatives were obtained in good yields with excellent enantioselectivity from the same reaction catalyzed cooperatively by the chiral triazole carbene and Ti(OPr-*i*)$_4$.[3d] On the other hand, the co-catalysis of chiral triazole carbenes and Lewis acids such as LiCl, Sc(OTf)$_3$, and Mg(OTf)$_2$ significantly improves the enantioselectivity of the reactions between α,β-unsaturated aldehydes and isatins or trifluoromethyl ketones.[3e,f] In addition, while the triazole carbene-catalyzed annulation reaction of enals with enones produced *trans*-substituted cyclopentenes as the major products, the same reaction yielded *cis*-substituted cyclopentenes under the catalysis of triazole carbene and Ti(OPr-*i*)$_4$.[3g] Furthermore, the imidazole carbene-catalyzed dimerization of α,β-unsaturated aldehydes proceeded preferentially with 1,2-addition of the homoenolate intermediates to the C═O of enals.[3h] On the contrary, however, the co-catalysis of imidazole or chiral triazole carbene with Ti(OPr-*i*)$_4$ reversed the regioselectivity to 1,4-addition.[3i] The cooperative NHC/Lewis acid catalysis strategy has recently been used in the total synthesis of *Securinega* alkaloids.[3j] Although cooperative catalysis of NHCs/Lewis acids has been shown to increase the efficiency and stereoselectivity, the regulation of reaction pathways by NHC/Lewis acid co-catalysis remains largely unknown.

Gravel and co-workers reported in 2011 the dimerization reaction of 2-formylcinnamate **1** catalyzed by a silyl ether substituted pyrrolotriazole carbene, affording 2,2′-(3,4,7,8-tetrahedrodibenzo[8]annulene)diacetate **3** via the sequential inter- and intramolecular Stetter reactions (Scheme 1, eq 1).[4]

Scheme 1. Reactions of 2-Formylcinnamates under Gravel's and Our Catalytic Conditions



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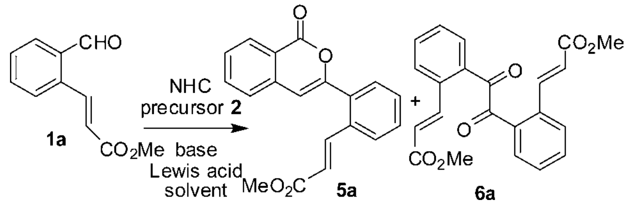
Our interest in NHC/Lewis acid cooperative catalysis led us to undertake the current study on the NHC/Lewis acid co-catalyzed reaction of 2-formylcinnamates. Remarkably, while the *N,N*-dialkyltriazole carbene-catalyzed dimerization of 2-formylcinnamates **1** produced a mixture of *cis*- and *trans*- 6,12-dihydroisochromeno[4,3-*c*]isochromene-2,2′-diacetates **4-I** and **4-II** via the sequential benzoin condensation and intramolecular oxa-Michael addition (Scheme 1, eq 2), the dimerization of 2-formylcinnamates **1** catalyzed by a combination of *N,N*-dialkyltriazole carbene and Ti(OPr-*i*)$_4$ followed a totally unexpected pathway to eliminate a $CHCO_2R$ moiety to furnish isochromenone derivatives **5** (Scheme 1, eq 3). We report herein the switch of reaction pathway affected by NHC/Lewis acid cooperative catalysis and an unprecedented elimination of acetate group under NHC catalysis.

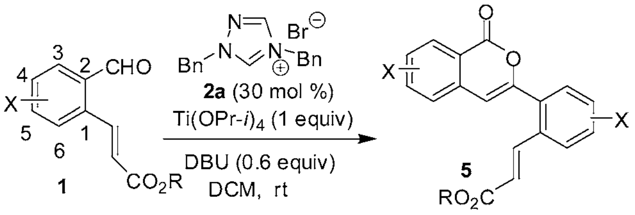
We initiated our study by examining the reaction of 2-formylcinnamate **1a** catalyzed by different catalysts under various conditions (see Scheme 2, and Table S1 in Supporting Information). In the presence of Ti(OPr-*i*)$_4$ in dichloromethane at ambient temperature, no reaction of methyl 2-formylcinnamate **1a** was observed except the partial transesterification of **1a** with isopropyl alcohol that was released from Ti(OPr-*i*)$_4$. Catalyzed by *N,N*-dibenzyltriazolylidene **2a′** (*N,N*-dibenzyltriazole carbene), 2-formylcinnamate **1a** was transformed into a mixture of *cis*- and *trans*-6,12-dihydroisochromeno[4,3-*c*]isochromene-6,12-diacetates **4a-I** and **4a-II** in a total 50% yield (**4a-I**:**4a-II** ~ 1.2:1) (Table S1, entry 2, Supporting Information). However, when a combination of *N,N*-dibenzyltriazolylidene **2a′** (30 mol %) and Ti(OPr-*i*)$_4$ (100 mol %) was used as the catalyst, the reaction led to the formation of 1,2-diketone **6a** and the fluorescent isochromenone derivative **5a**, and compound **6a** was converted gradually into **5a** in an elongated period. After 24 h, isochromenone **5a** was isolated in 62% yield along with a trace amount of 1,2-dione **6a** (Table S1, entry 3) (see single-crystal structures of **4a-II**, **5a**, and **6a** in the Supporting Information). It was noteworthy that the replacement of *N,N*-dibenzyltriazole carbene **2a′** with *N,N*-dimethyltriazole carbene **2b′**, *N*-phenylpyrrolo[2,1-*c*]triazole carbene **2c′**, thiazole carbene **2d′**, and imidazole carbene **2e′** resulted in diminished chemical yields of product **5a** (see Table S1, Supporting Information). The chemical yield of **5a** decreased to 41% when the loading of carbene **2a′** was lowered to 20 mol %. In refluxing dichloromethane, partial transesterification of methyl cinnamate **5a** with isopropyl alcohol that was released from Ti(OPr-*i*)$_4$ occurred to afford a mixture of **5a** (R = Me) and **5a′** (R = *i*-Pr) in a total yield of 61%. Decreasing the reaction temperature to 0 °C slightly affected the efficiency of catalysis. The reaction conditions were further optimized by varying Lewis acids, solvents, and bases that were used to generate carbene catalyst. It seemed that the use of either other Lewis acids including $Ti(OCH_3)_4$, $Fe(OAc)_2$, $Cu(OTf)_2$, and Mg(OBu-*t*)$_2$ or other bases such as NaH, DABCO, *t*-BuOK, and Cs_2CO_3 did not improve the formation of product **5a**. Employment of other solvents like acetonitrile, acetone, THF, and toluene instead of DCM led disappointingly to a decrease of product **5a** (see Table S1, Supporting Information).

Scheme 2. Optimization of Reaction Conditions



With the optimized conditions in hand, the substrate scope was surveyed by varying aldehydes **1** attached by different substituents. It was found that the chemical yields of products **5** were marginally affected by the alkyl groups of ester moiety of 2-formylcinnamates **1**. Under the catalysis of *N,N*-dibenzyltriazolylidene **2a′** and Ti(OPr-*i*)$_4$, for instance, methyl (**1a**), isopropyl (**1b**), and benzyl 2-formylcinnamate (**1c**) produced the corresponding 2-(1-oxoisochromen-3-yl)cinnamates **5a**, **5b**, and **5c** in 50–63% yields (Table 1, entries 1–3). On the other hand, both the nature of substituents and their substitution pattern on the benzene ring of substrates **1** strongly influenced the reactivity of aldehydes **1** and the intermediate 1,2-diones **6**. For example, 3-fluoro- (**1d**), 5-fluoro- (**1f**), and 5-chloro-2-formylcinnamate (**1h**) produced higher yields of the corresponding products **5d**, **5f**, and **5h** (60%–68%) in comparison with 4-fluoro-2-formylcinnamate **1e** and 4-chloro-2-formylcinnamate **1g**, which give products **5e** and **5g** in only 47% and 40% yields, respectively (Table 1, entries 4–8). In addition, when the 2-formylcinnamates **1i–k** were substituted by electron-donating methyl and methoxy groups, both the reaction of **1i–k** and the transformation of intermediates **6i–k** were less efficient. The products **5i–k** were isolated in lower yields (35%–48%) along with the unconsumed reactants **1i–k** and intermediates **6i–k**, and even the reaction was elongated to 24–48 h (Table 1, entries 9–11).

Table 1. Reaction of 2-Formylcinnamates 1 under the Catalysis of *N,N*-Dibenzyltriazolylidene and Ti(OPr-*i*)$_4$

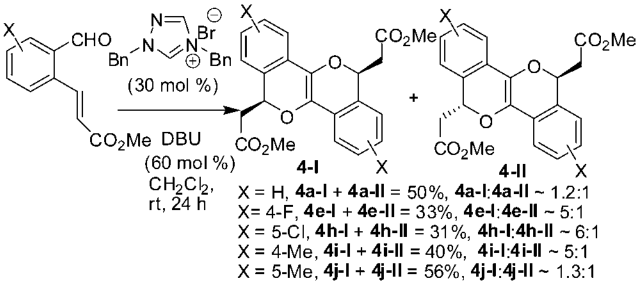


entry	1	X	R	time (h)	5^a (%)
1	**1a**	H	Me	24	**5a** (62)
2	**1b**	H	*i*-Pr	24	**5b** (50)
3	**1c**	H	Bn	12	**5c** (63)
4	**1d**	3-F	Me	12	**5d** (60)
5	**1e**	4-F	Me	12	**5e** (47)
6	**1f**	5-F	Me	22	**5f** (68)
7	**1g**	4-Cl	Me	22	**5g** (40)
8	**1h**	5-Cl	Me	22	**5h** (63)
9	**1i**	4-Me	Me	24	**5i** (48)^b
10	**1j**	5-Me	Me	48	**5j** (35)^b
11	**1k**	4-OMe	Me	48	**5k** (40)^b

[a] In addition to products **5**, a trace amount of byproducts was also detected without isolation. [b] Both reactants **1i–k** and intermediates **6i–k** were not completely consumed.

The generality for the formation of isochromeno[4,3-*c*]isochromene-6,12-diacetates **4-I** and **4-II** was also tested. Scheme 3 shows that all fluorine-, chlorine-, or methyl-substituted 2-formylcinnamates **1** underwent the NHC-catalyzed dimerization in dichloromethane at ambient temperature to produce a mixture of *cis*- and *trans*-isochromeno[4,3-

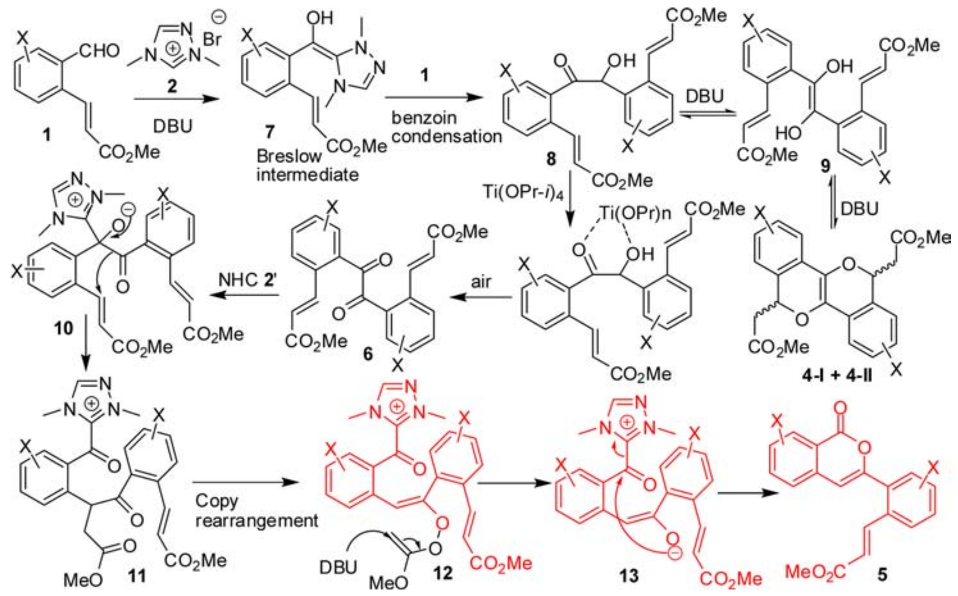
Scheme 3. *N,N*-Dibenzyltriazole Carbene-Catalyzed Reaction of 2-Formylcinnamates 1



c]isochromene-6,12-diacetates **4-I** and **4-II** in total yields of 31%−56%. Determined by ^{1}H NMR, the ratios of *cis*-isomers **4-I** over the *trans*-isomers **4-I** in the crude products isolated by chromatography were in the range of 1.2:1−6:1. Notably, the *cis*-isomers **4-I** underwent spontaneous partial isomerization into *trans*-isomers **4-II** while recrystallizing in organic solvents such as THF, ethyl acetate, *n*-hexane, and chloroform. As a consequence, *trans*-isomers **4-II** could be obtained from the recrystallization of the *cis*-isomers **4-I** or a mixture of *cis*- and *trans*-isomers in some cases. This has been exemplified by the isolation of **4h-II** from recrystallization of **4h-I** in THF and *n*-hexane and by the precipitation of **4a-II** or **4j-II** from the recrystallization of the corresponding mixture of two diastereoisomers.

Structures of all products were elucidated on the basis of spectroscopic data and single-crystal X-ray diffraction analysis. It is interesting to note that products **5** were constructed from two 2-formylcinnamates **1** with the loss of a $CHCO_2R$ moiety. The formation of an isochromenone ring along with the cleavage of an acetate moiety from the NHC/Lewis acid catalyzed reaction of 2-formylcinnamates **1** was very intriguing. To shed light on the reaction mechanism, the reaction of 2-formylcinnamate **1a** was carefully monitored by means of TLC, ^{1}H NMR spectroscopy, and GC−MS analysis. Monitored by TLC analysis, in the presence of *N,N*-dibenzyltriazolylidene **2a′** and Ti(OPr-*i*)$_4$, the reaction of **1a** initially formed 1,2-diketone **6a** in 10 min (**6a** was indeed isolated in 22% yield by quenching the reaction with water at this time). Formation of isochromenone **5a** in addition to *α*-diketone **6a** was detected in 30 min. With the progress of the reaction, the resulting diketones **6** were gradually transformed into 2-(1-oxoisochromen-3-yl)cinnamates **5**. Sakaguchi et al. have reported the synthesis of 1,2-diaryl-1,2-diketones from NHC-catalyzed benzoin condensation of arylaldehydes under aerobic oxidation conditions.[5] Since 1,2-diketones **6** might be generated due to the oxidation of the benzoin products, the NHC/Ti(OPr-*i*)$_4$-catalyzed reactions of **1a** were then conducted and compared under nitrogen, oxygen, and atmospheric conditions. In comparison to the reaction under nitrogen protection, the reaction under atmospheric conditions provided a lower yield of product **5a** (45%), due to probably the hydrolysis of Ti(OPr-*i*)$_4$ in air. The reactions under oxygen and nitrogen atmosphere produced similar yields of product. In the studies on the transformation of 1,2-diketone **6a**, it was evidenced that the dibenzyltriazolylidene **2a′** alone was able to convert **6a** into **5a** in 23% yield after reacting for 24 h in dichloromethane at room temperature. The cooperative catalysis of carbene **2a′** and Ti(OPr-*i*)$_4$ was found to facilitate this transformation, and **5a** was obtained in 45% yield in 5 h under the same conditions. To clarify an ionic or radical mechanism in the transformation of diketones **6** to isochromenones **5**, the carbene **2a′**/Ti(OPr-*i*)$_4$-catalyzed reaction of **6a** was also conducted in the dark. Product **5a** was obtained in similar yields (42% and 45%) from the reactions in the absence and the presence of light under the same conditions, which indicated the irrelevance of the reaction to a radical process. A crossover experiment showed convincingly that the transformation of diketones **6** to isochromenones **5** proceeds via an intramolecular rearrangement fashion, as the reaction starting from a mixture of **6a** and **6i** (**6a**:**6i** = 1:1) produced no crossover products derived from both species of **6a** and **6i** according to GC−MS analysis of the reaction mixture.

Scheme 4. Proposed Mechanisms for the Formation of Isochromeno[4,3-*c*]isochromene-6,12-diacetates 4 and 2-(1-Oxoisochromen-3-yl)cinnamates 5 from 2-Formylcinnamates 1



Taking the aforementioned outcomes into consideration, the plausible mechanism for the formation of 2-(1-oxoisochromen-3-yl)cinnamates **5** from 2-formylcinnamates **1** is proposed in Scheme 4. Being different from the Gravel's dimerization of 2-formylcinnamate **1a**, which started from the addition of the Breslow intermediate derived from a bulk triazolylidene and aldehyde **1a** to the C=C bond of α,β-unsaturated ester of **1a** (a Stetter reaction),[4] the dimerization of 2-formylcinnamates **1** catalyzed by *N*,*N*-dialkyltriazolylidene **2′** is initiated most likely from the addition of Breslow intermediates **7** to the C=O bond of aldehydes **1** to generate α-hydroxyl ketones **8** (a benzoin condensation). In the absence of Ti(OPr-i)$_4$, α-hydroxyl ketones **8** would tautomerize into enols **9**, which undergo base-catalyzed intramolecular oxa-Michael addition to yield the *cis*- and *trans*-isochromeno[4,3-*c*]isochromene-6,12-diacetates **4-I** and **4-II**. In the presence of Ti(OPr-i)$_4$, the complexation of α-hydroxyl ketones **8** with Ti(OPr-i)$_4$ inhabits their intramolecular cyclization, and the oxidation of **8** by air leads to the formation 1,2-diketones **6**. The transformation of diones **6** to products **5** is especially intriguing. Possibly, a nucleophilic addition of triazolylidene to the carbonyl of diones **6** causes the intramolecular rearrangement of **6** to form carbanion intermediates **11**. Compound **11** probably undergoes a Copy rearrangement to give the peroxide intermediates **12**. The driving force of the Copy rearrangement might be attributed to the formation of a large π-conjugated system of **12** (see the red moiety of **12** in Scheme 4). The cleavage of peroxides **12** is probably initiated by the addition of a nucleophile, such as DBU, to the C=C bond, which results in the enolates **13**. Intramolecular lactonization of **13** affords finally 2-(1-oxoisochromen-3-yl)cinnamates **5**.

In summary, we have shown the dimerization reactions of 2-formylcinnamates catalyzed by NHC catalysts and by the cooperative NHC/Lewis acid catalysts. While the triazole carbene-catalyzed dimerization of 2-formylcinnamates underwent benzoin condensation followed by intramolecular oxa-Michael addition to afford isochromeno[4,3-*c*]isochromene products, under the cooperative catalysis of triazole carbene and Ti(OPr-i)$_4$, the dimerization of 2-formylcinnamates proceeded through a completely different route to furnish the formation of isochromenone derivatives with an unusual elimination of an acetate moiety. This work substantiates the diversity of NHC catalysis and the control of reaction pathway using a NHC/acid dual catalytic strategy, extending the application of N-heterocyclic carbene and Lewis acid cooperative catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Table of optimization of reaction conditions, experimental details, characterization of products, copies of ^{1}H NMR and ^{13}C NMR spectra of products, and single-crystal data of **4a-II**, **5a**, and **6a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ycheng2@bnu.edu.cn. Tel: +86-10-58805558. Fax: +86-10-58805558.

Author Contributions

†H.-Y.D. and Z.-T.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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