Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.202000313

Link to VoR: https://doi.org/10.1002/adsc.202000313

10.1002/adsc.202000313

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Fe(III)-Catalyzed, Cyclizative Coupling between 2-Alkynylbenzoates and Carbinols: Rapid generation of Polycyclic Isocoumarins and Phthalides and Mechanistic Study

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Received: ((will be filled in by the editorial staff))

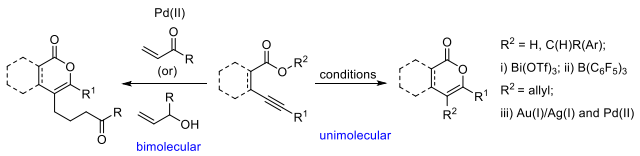
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. $FeCl_3$ catalyzed, highly regioselective cyclizative coupling of internal alkynes with alcohols has been reported for the rapid synthesis of structurally divergent, complex isocoumarins and phthalides respectively in intermolecular and intramolecular fashion. This strategy exhibited very high substrate scope and efficiency and proceeds through the simultaneous formation of C–O and C-C bonds. Observations from a series of control experiments supported a) the mechanism as Lewis acid catalyzed dual activation of ester and alcohol, b) the role of carbocation for the enhanced rates of cyclization, i.e., activation of alkyne by carbocation, and c) no role of HCl in the reported cascade process.

Keywords: Isocoumarins; Domino cyclizations; Phthalides; 2-alkynylbenzoates; Lewis acid catalysis

Introduction

The electrophilic activation-nucleophilic addition based cascade processes of alkynes in presence of Lewis acid catalysts continue to be a fascinating area of research in organic synthesis. These strategies provide simultaneous construction of multiple C-C, C-O and C-N bonds, thereby an opportunity to build the complexity in a rapid and efficient manner.[1] The 2-alkynylbenzoates and α-alkynylenoates have been well utilized as building blocks for the synthesis of isocoumarins(pyrones) as well as phthalides(butenolides) under Lewis acid and transition metal catalysis.[2] They have also been used in the generation of C-4 functionalized isocoumarins with non-carbon electrophilic trapping such as SR, SeR, X etc.[3] In contrast, simultaneous creation of isocoumarins followed by functionalization of C-4 position with carbon electrophiles has been less explored in the literature.[4] The research groups of Komeyama and Melen have reported a Lewis acid [$Bi(OTf)_3$ and $B(C_6F_5)_3$ respectively] catalyzed intramolecular migration of alkyl group from ester to C-4 position of the isocoumarin (Scheme 1).[4a],[4b] A dual (co-operative) catalysis based intramolecular migration of allyl group has also been reported, in presence of Au(I)/Pd(II) catalytic systems for the synthesis of C-4-alkylated isocoumarins.[4c] Several, Pd(II)-catalyzed bimolecular reactions with olefins *via* Heck-type oxidative coupling were also known.[4d-4h]



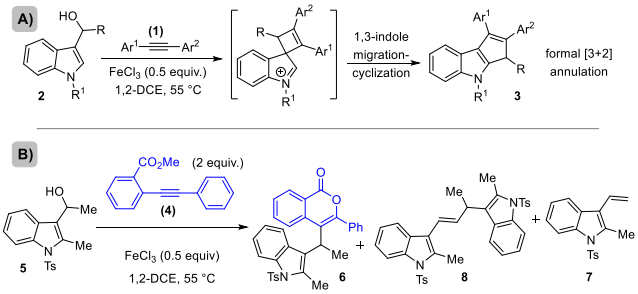
Scheme 1. Known methods for the C4-alkylated isocoumarins from 2-alkynylbenzoates/alkynylenoates.

Nonetheless, to the best of our knowledge, the cyclizatve coupling between the methyl 2-alkynylbenzoates/α-alkynylenoates and alcohols either in an intramolecular or intermolecular fashion is not reported so far.

In continuation of our interest in the exploration of novel reactivity's of alkynes and propargylic alcohol derivatives,[5],[6] here in we discovered and developed a $FeCl_3$ catalyzed, cascade cyclizative-coupling process between methyl 2-alkynylbenzoates (α-alkynylenoates) and alcohols. This process can be operational both in intermolecular and intramolecular

versions and provide access to structurally novel, complex 4-C-substituted isocoumarins (pyrones) as well as phthalides (butenolides) under mild reaction conditions. The design, discovery and development constitutes the current manuscript

Recently we reported a $FeCl_3$ promoted, formal [3+2]annulation of diarylalkynes **1** and indole-3-carbinols **2** for the synthesis of cyclopenta[*b*]indole **3** (Scheme 2A). In continuation, when we employed a diarylalkyne possessing an *o*-methyl carboxylate group **4**, against the alcohol **5**, a new product, an isocoumarin **6** was isolated (34%) along with the 3-vinylindole[7] **7** (14%) and its dimer **8** (10%). (Scheme 2B) Delighted by the fortuitous observation, we aimed to pursue this transformation in systematic manner.

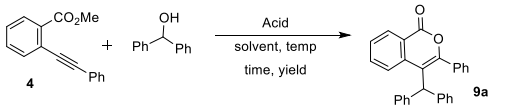


Scheme 2. A) Coupling of indole-3-carbinols and alkynes for cyclopenta[*b*]indoles (Earlier work); B) Discovery of new mode of reactivity for substituted isocoumarins (This work).

Results and Discussion

We started our investigation employing 2-alkynylbenzoate **4** (possessing phenyl group on the alkyne terminus) as a model substrate against diphenylmethanol. Treatment of a mixture of **4** and alcohol (1 equiv.) in 1,2-DCE with MsOH (20 mol%) at 50 °C (entry 1, Table 1) gave the expected isocoumarin **9a** as the exclusive product, *via* a *6-endo-dig* cyclization–coupling cascade, in 68% yield after 10 h. There was no detection of any traces of the corresponding phthalide (*via 5-exo-dig* cyclization). Employing other Brønsted acids (entries 2 & 3) such as, *p*TSA (20 mol%) and TfOH (20 mol%) resulted in poor yields (50% & 40%; 24 h & 2.5 h) of **9a** respectively. On the other hand, employing $FeCl_3$ (20 mol%, entry 4,) gave 71% yield of **9a** after 4 h at 50 °C along with 20% of the unreacted **4**. Increasing the temperature to 80 °C gave the improved yield (75%) for **9a** with shorter reaction time (1.5 h) along with 20% of **4**. Next increase in amount of alcohol (1.3 equiv.) with $FeCl_3$ (20 mol%) and at 80 °C (entry 6), further improved the yield of **9a** to 82% with complete consumption of **4**. A gradual decrease in amounts of $FeCl_3$ to 10 mol% and 5 mol% (entries 7 & 8) resulted in 88% and 90% respective yields of **9a** after 1 h and 1.25 h, at 80 °C. Further decrease to 2 mol% (entry 9, Table 1) hampered the reaction efficiency (60%). We next performed the reaction in various solvents employing 5 mol% of $FeCl_3$, and 1.3 equiv. of alcohol at 80 °C (entries 10-13). Both 1,2-DCB and CH_2Cl_2 gave 85% and 82% respective yields of product **9a** (entries 10 & 11). Whereas in $CHCl_3$ and toluene (entries 12 & 13), reactions were slow (9 h and 24 h) and resulted in reduced yields (68% & 51%) for **9a** along with 20% and 30% of unreacted starting material **4**, respectively.

Table 1. Optimization Study.



S.No.	Acid	mol%	R-OH (equiv.)	solvent	Temp. (°C)	Time (h)	Yield (%)[h]
1[a]	MsOH	20	1.0	1,2-DCE	50	10	68
2[b]	PTSA	20	1.0	1,2- DCE	50	24	50
3	TfOH	20	1.0	1,2-DCE	50	2.5	40
4[c]	$FeCl_3$	20	1.0	1,2-DCE	50	4	71
5[d]	$FeCl_3$	20	1.0	1,2-DCE	80	1.5	75
6	$FeCl_3$	20	1.3	1,2-DCE	80	2	82
7	$FeCl_3$	10	1.3	1,2-DCE	80	1	88
8	$FeCl_3$	5	1.3	1,2-DCE	80	75 min	90
9[e]	$FeCl_3$	2	1.3	1,2-DCE	80	5.5	60
10	$FeCl_3$	5	1.3	1,2-DCB	80	0.5	85
11	$FeCl_3$	5	1.3	CH_2Cl_2	80	2.5	82
12[f]	$FeCl_3$	5	1.3	$CHCl_3$	80	9	68
13[g]	$FeCl_3$	5	1.3	toluene	80	24	51

[a] 10%, [b] 30%, [c] 20%, [d] 20%, [e] 10%, [f] 20%, [g] 30% of **4**, [h] isolated yields

So the optimized condition for the discovered bimolecular cyclizative coupling of 2-alkynylbenzoates with alcohols is, alcohol (1.3 equiv.), $FeCl_3$ (5 mol%), 1,2-DCE and 80 °C (entry 8, Table 1). We next focused to evaluate the strength and weakness of this methodology. Initially we screened various alcohols against the **4** (Scheme 3). Structurally divergent biaryl as well as aryl-alkyl carbinols have been successfully employed under standard reaction conditions to generate library of novel isocoumarin derivatives **9b-h** in excellent yields (70-85%). In case of indole-3-carbinols, the reactions were very fast, but yields of the coupled products **9i-j, 6** were relatively poor (45-50%). We also employed aryl-propargyl as well as aryl-allyl alcohols. In both the cases, expected coupled isocoumarins **9k** (42%, NMR yield) and **9l** (65%, NMR yield) were isolated as inseparable mixture with the simple isocoumarin **10**, along with ~30% of ester **4**. In addition to the spectroscopic data, the presence of the coupled isocoumarin frame work has also been unambiguously confirmed by the single crystal X-ray diffraction analysis of the compound **6** (Scheme 3).[8]

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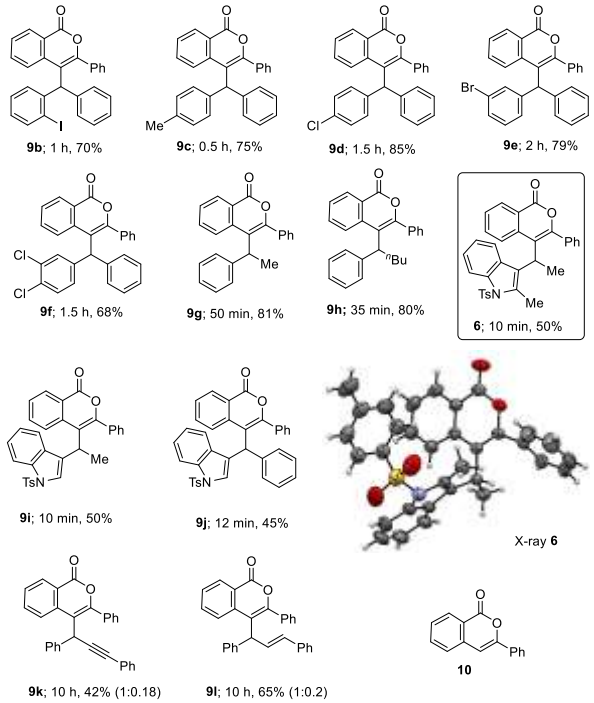
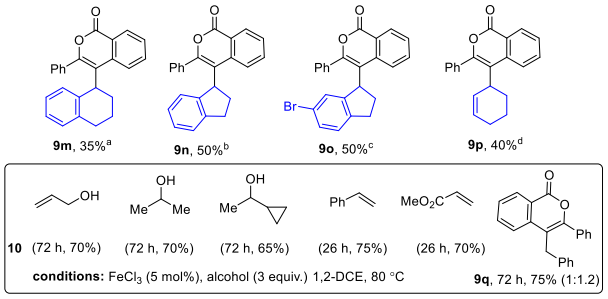


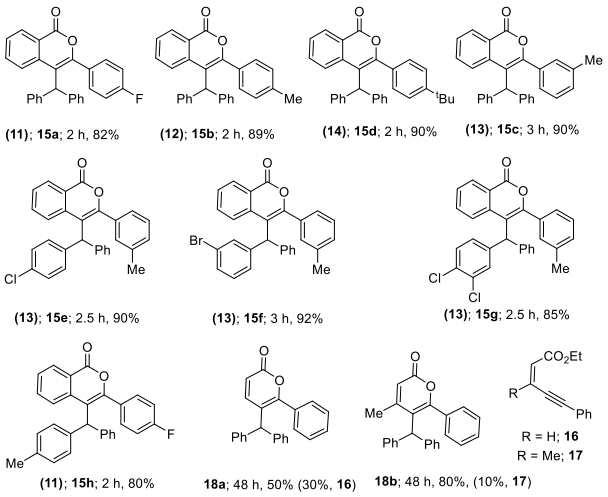
Scheme 3 Scope study for alcohols and ORTEP diagram for compound **6**; **conditions**: ester **4** (1 equiv.), $FeCl_3$ (5 mol%), alcohol (1.3 equiv.), 1,2-DCE, 80 °C.

In continuation, various bicyclic benzylic alcohols have also been employed as coupling partners (Scheme 4). When the reactions were performed with alcohols (2 equiv.) and the 2-alkynylbenzoate **4**, with 5 mol% of $FeCl_3$, at RT[9] resulted in the formation of expected coupled isocoumarins **9m-p** as exclusive products but the conversions were poor even after 24 h. In all cases variable amounts of unreacted benzoate **4** was isolated. Further, dialkylcarbinols, primary alcohols (allylic and benzylic), styrene and methyl acrylate have also been employed as electrophilic carbon partners for the cyclizative coupling reaction under standard conditions. In all cases, except the benzylic alcohol, there was only cyclization reaction observed to give the corresponding simple isocoumarin **10** (65-75% yields) after 72 h, and no traces of coupling products were observed. In contrast benzyl alcohol underwent the coupling reaction to give a (1:1.2) inseparable mixture of the coupled isocoumarin **9q** and simple isocoumarin **10**. It is noteworthy to mention here that, all the above reactions (though underwent simple cyclization) are very slow and took about 72 h for the complete consumption of the starting 2-alkynylbenzoate **4**. This might suggests that, the stable carbocationic intermediate (generated from Lewis acid and alcohol) is necessary for the activation of the alkyne to promote the efficient cyclization process as well as coupling with enhanced reaction rates.



Scheme 4 Screening bicyclic and aliphatic carbinols. **conditions**: ester **4** (1 equiv.), $FeCl_3$ (5 mol%), alcohol (2 equiv.), 1,2-DCE, RT, 24 h; [a] 60%; [b] 48%; [c] 45%; [d] 55% of starting material **4**

Subsequently, we have also studied the scope of substituted aryl groups on alkyne of 2-alkynylbenzoates **11-14** against various alcohols (Scheme 5). All the substrates underwent a smooth and highly efficient cyclizative-coupling to afford the corresponding structurally divergent 3,4-dialkylated(arylated) isocourmarin derivatives **15a-h**. During this study we did not observe any electronic as well as positional effect of substituents present on the arene. With the acyclic α-alkynyl-enoates **16** & **17**, the reactions found to be relatively slow and even after 48 h at 80 °C, variable amounts (30% and 10% respectively) of enaotes **16** & **17** were recovered along with the poly-substituted pyrenones **18a** (50%) and **18b** (80%).



Scheme 5 Diversity of alkyne substituent's and tethers. **Conditions**: ester (1 equiv.), $FeCl_3$ (5 mol%), alcohol (1.3 equiv.), 1,2-DCE, 80 °C.

Surprisingly, placing an alkyl group on the alkyne terminus promoted a highly regio-selective 5-*exo-dig* cyclization-coupling cascade to generate the complex phthalide derivatives **19a-c** in good yields (Scheme 6). This might be due to the more stabilized carbocationic (benzylic) character at the internal

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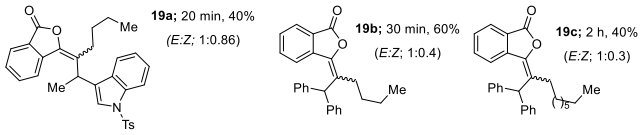
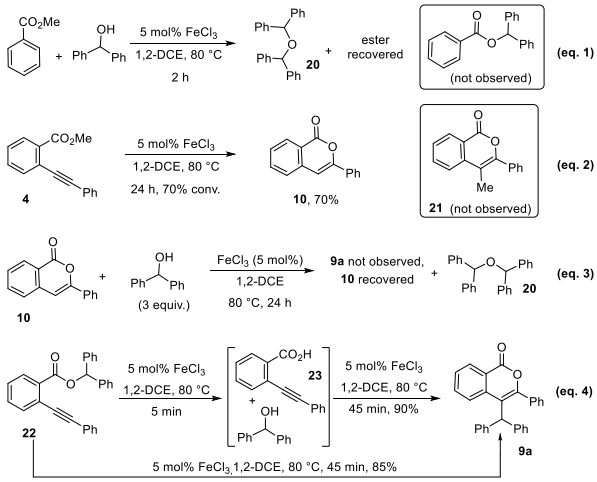
carbon of the alkyne. In all cases a diastereomeric (*E*/*Z*) mixture was isolated.



Scheme 6 Regioselectivity reversal with alkyl-substituents on alkyne for the selective generation of 3-ylidene-phthalides

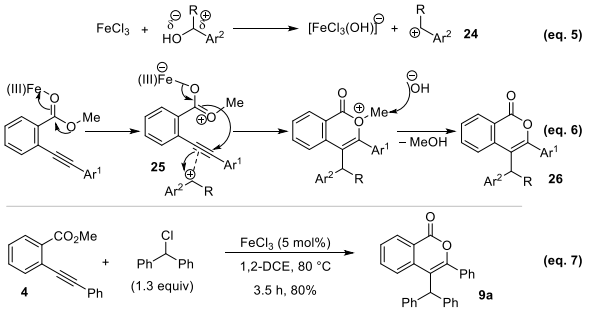
To get some insights into the mechanistic details of this cascade process, we performed several control experiments (Scheme 7). To verify the possibility of a *trans*-esterification followed by intramolecular alkyl group migration, we treated the simple methyl benzoate (lacks the alkyne at *ortho*- position) with the diphenyl alcohol under standard reaction conditions (eq. 1). The *trans*-esterification was not observed; instead the corresponding ether **20** was isolated[10] along with unreacted methyl benzoate. Next, we subjected **4** to standard reaction conditions, but in the absence of any of the alcohol partner (eq. 2). This resulted in an exclusive formation of the simple isocoumarin **10** (70%) with only 70% conversion of **4**, even after 24 h at 80 °C. No traces of the 4-methyl-isocoumarin **21** was identified. The observed slower reaction rate for the formation **10** again (compare with Scheme 4) suggests the requirement for the possible electrophilic activation of alkynes by the carbocation intermediate (generated from alcohol), which lacks in the absence of alcohol in the reaction mixture.



Scheme 7 Control experiments

Further, treatment of the isocoumarin **10** with diphenyl alcohol, under standard reaction conditions (eq. 3), failed to produce any of the coupled isocoumarin **9a**, instead the ether **20** was isolated along with unreacted isocoumarin **10**. We also prepared a diphenyl carbinol ester **22**, and subjected to standard reaction conditions (eq. 4). Surprisingly, after 5 min (workup with water), it gave a mixture of acid **23** and alcohol through hydrolysis, whereas after 45 min, directly gave the expected product **9a** in 85% yield. On the other hand treatment of the mixture of acid and alcohol with standard reaction conditions, also gave the product **9a** (90%). These observations suggests that, a) there is no trans-ester formation under reaction conditions, i.e., intramolecular alkyl group migration,[4b] b) the reaction does not involve a step wise C-O bond (isocoumarin formation) followed by C-C bond formation (coupling) rather undergoes a simultaneous construction of both the C-O as well as C-C bonds, and c) presence of alcohol, i.e., carbocationic species has influence on the rate of the cyclization.

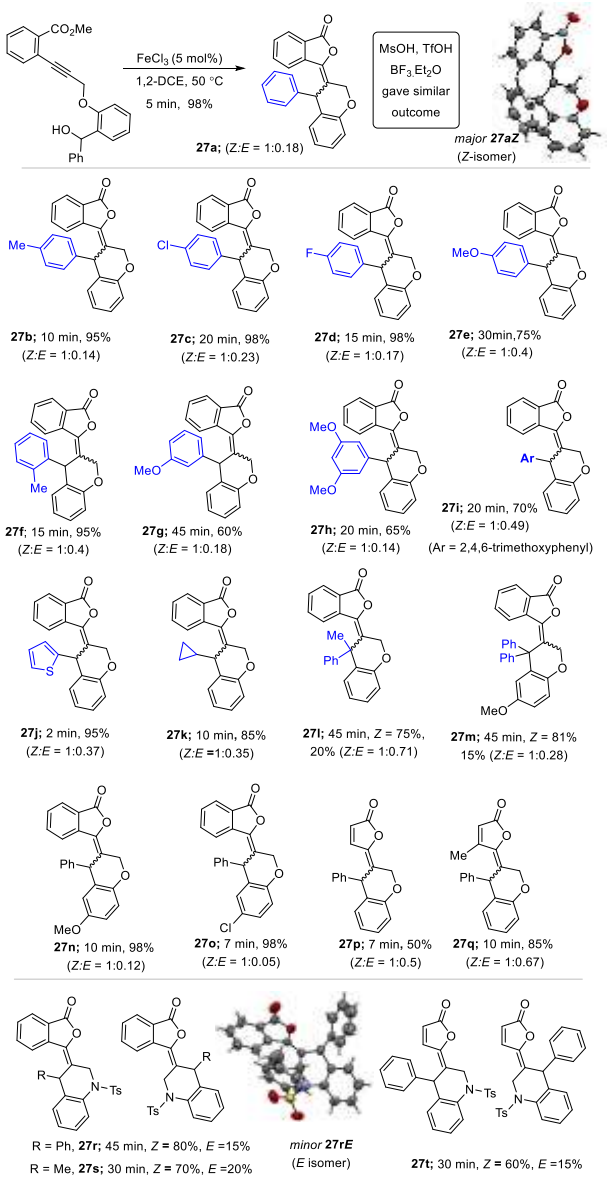
Based on these observations, we proposed a suitable mechanism for the discovered bimolecular cyclizative coupling process (Scheme 8). Initial activation of both alcohol and ester by the acid generates carbocation species **24** and a zwitter ionic species **25** (Scheme 8, eq. 5 & 6).[4b] Next activation of the alkyne by electrophilic carbocation[11] **24** and *6-endo-dig* attack by the ester, followed by demethylation by hydroxide ion gives the coupled-isocoumarin **26**. To verify the presence of HCl (if any) under reaction conditions and its role in the observed reactivity with alcohols, we performed the reaction with diphenylmethyl chloride in place of corresponding alcohol under anhydrous conditions (Scheme 8, eq. 7). Here since no hydroxide is present, no possibility for HCl formation under reaction conditions. Delightfully, the reaction is clean and gave the product **9a** in 80% yield (eq. 7). This observation rules out the presence as well as catalytic role of HCl during the standard reaction conditions.



Scheme 8 Proposed mechanism and control experiment to rule out the role of HCl

After studying the bimolecular coupling of methyl 2-alkynylbenzoates and α-alkynylenoates with alcohols and understanding the mechanistic details of this process, we next planned to develop the corresponding intramolecular version (Scheme 9) for the generation of polycyclic systems *via* a domino,

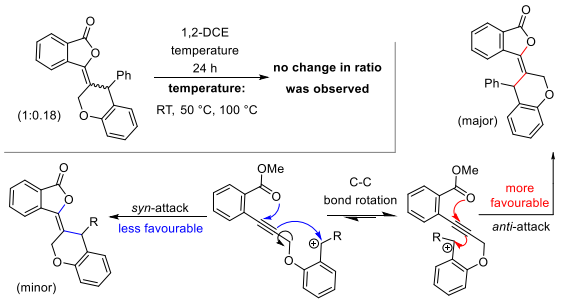
double-cyclization strategy i.e., lactonization–intramolecular coupling.



Scheme 9 a) Intramolecular domino-cyclizative coupling of alkynes and alcohols; b) ORTEP diagrams for the compounds **27aZ** (major) and **27r*E*** (minor).

Accordingly, various structurally divergent methyl 2-alkynylbenzoates, possessing intramolecular aryl carbinols tethered through an alkyl chain, have been employed under standard reaction conditions. Since the reactions found to be quicker and completed in <5 min., we decreased the reaction temperature from 80 °C to 50 °C for these intramolecular substrates. All the substrates smoothly underwent the cascade cyclization to generate the corresponding phthalide based polycyclic hybrid structures **27a-m** in excellent yields (up to 98%) within 5-45 min at 50 °C.

In all cases an inseparable mixture of two diastereomers (*E*- and *Z*-) across the newly generated *exo*-olefin has been obtained, with the *Z*-isomer being the major. A single crystal X-ray diffraction analysis of the major isomer of the compound **27a*Z***, unambiguously confirmed the presence of the chromene based phthalide framework.[12] Further, we have employed substrates varying in the nature of tethered aryl group and also acyclic substrates, i.e., *Z*-enynoates for the generation of corresponding polycyclic phthalides **27n-o** and butenolides **27p-q** in good yields. Nitrogen tethered 2-alkynylbenzoate-alcohols were also employed for the generation tetrahydroquinoline based phthalides **27r-t** (Scheme 9). Noteworthy to mention here that, in all three cases, the *Z*- (**27r*Z*-27t*Z***; major) and *E*-isomers (**27r*E*-27t*E***) were separable on column chromatography, in contrast to their oxygen counterparts. A single crystal X-ray diffraction analysis of the minor isomer of the compound **27r*E***, unambiguously confirmed the presence of the tetrahydro-quinoline based phthalide framework.[13]



Scheme 10 Rationale for the observed *E/Z*-mixtures

The two stereoisomers across the *exo*-olefin, can be formed either from two parallel trapping reactions or they are inter-convertible under reaction conditions. In order to verify and distinguish between these two possibilities, a (1: 0.18; *Z:E*) mixture was heated at various temperatures and observed no change in the ratio. This observation suggests that, the two products (*Z*- and *E*-isomers) may be forming during the reaction *via anti*-and *syn*- trapping of the carbocation respectively.

Conclusion

In conclusion, a $FeCl_3$ catalyzed, highly regioselective cyclizative coupling of internal alkynes with alcohols has been developed for the selective, rapid and efficient synthesis of structurally divergent, complex isocoumarins and phthalides. This process is operable both in an intermolecular and intramolecular fashion and involves the simultaneous construction of both C–O and C-C bonds. This process exhibits a very broad array of substrate scope with excellent yields. Control experiments supported a) the mechanism as Lewis acid catalyzed dual activation of ester and

alcohol, b) the role of carbocation for the enhanced rates of cyclization, i.e., possible activation of alkyne by carbocation, and c) no role of HCl in the reported cascade process.

Experimental Section

General procedure for the synthesis of substituted isocoumarin derivatives

To a solution of the ester (1 equiv.) in 1,2-dichloroethane (1,2-DCE) (5 ml/0.21 mmol, 0.04 *M*), alcohol (1.3 equiv.) under nitrogen atmosphere was added $FeCl_3$ (0.05 equiv.). The reaction tube was stirred at 80 °C in oil bath for 30 min-24 h. After completion of the reaction (by TLC analysis), saturated $NaHCO_3$ and CH_2Cl_2 were added to reaction mixture and extracted with CH_2Cl_2. The crude material was purified by column chromatography to yield the corresponding isocoumarin derivatives.

General procedure for the synthesis of phthalides derivatives

To a solution of the hydroxy-ester (1 equiv.) in 1,2-dichloroethane (3 ml/0.13 mmol, 0.04 *M*) under nitrogen atmosphere was added $FeCl_3$ (5 mol%). The reaction tube was stirred at 55 °C for 5-30 min. After completion of the reaction (by TLC analysis), saturated $NaHCO_3$ and CH_2Cl_2 were added to reaction mixture and extracted with CH_2Cl_2. The crude material was purified by flash column chromatography to yield the corresponding phthalides derivatives.

Acknowledgements

We thank Indian Institute of Technology Madras, Chennai for infrastructural facility. We thank SERB-INDIA, for financial support through CRG/2019/000988. SG thanks IIT Madras for HTRA fellowship

References

[1] a) A. Balog, S. V. Geib, D. P. Curran, *J. Org. Chem.***1995**, *60*, 345-352; b) U. Jana, S. Biswas, S. Maiti, *Eur. J. Org. Chem*. **2008**, 5798-5804; c) S. Biswas, S. Maiti, U. Jana, *Eur. J. Org. Chem*. **2009**, 2354-2359; d) Z. Liu, J. Wang, Y. Zhao, B. Zhou, *Adv. Synth. Catal*. **2009**, *351*, 371-374; e) L. Chen, L. Yu, Y. Deng, Y. Cui, G. Bian, J. Cao, *Org. Biomol. Chem*. **2016**, *14*, 564-569; f) L. K. Kinthada, K. N. Babu, D. Padhi, A. Bisai, *Eur. J. Org. Chem*. **2017**, 3078-3091; g) R. R. Naredla, D. A. Klumpp, *Chem. Rev.* **2013**, *113*, 6905-6948; h) R. Kumara, E. V. V. D. Eycken, *Chem. Soc. Rev*., **2013**, *42*, 1121-1146; i) D. Lebœuf, V. Gandon, *Synthesis* **2017,** *49*, 1500-1508; j) I. Bauer, H.-J. Gandon *Chem. Rev.* **2015**, *115*, 3170-3387; k) S. Schroeder, C. Strauch, N. Gaelings, M. Niggermann, *Angew. Chem. Int. Ed*. **2019**, *58*, 5119-5123; l) S.-T. Yuan, Y.-H. Wang, J.-B. Liu, G. Qiu, *Adv. Synth. Catal.* **2017**, *359*, 1981-1989; m) Y.-C. Wang, R.-X. Wang, G. Qiu, H. Zhou, W. Xiec, J.-B. Liu, *Org. Chem. Front.* **2019**, *6*, 2471-2479; n) Y.-C. Wang, J.-B. Liu, H. Zhou, W. Xie, P. Rojsitthisak, G. Qiu, *J. Org. Chem.* **2020**, *85*, 1906-1914; o) Z. Lei, Y. Si-Tian, W. Peng, L. Jin-Biao, *Chin. J. Org. Chem.*, **2020**, *40*, ASAP. doi: 10.6023/cjoc201912029.; p) X. Zhang, X. Wan, Y. Cong, X. Zhen, Q. Li, D. Zhang-Negrerie, Y. Du, K. Zhao, *J. Org. Chem.* **2019**, *84*, 10402-10411; q) B. S. Chinta, H. Sanapa, K. P. Vasikarla, B. Baire, Org. Biomol. Chem. **2018**, *21*, 3947-3951.

[2] a) H. Sashida, A. Kawamukai, *Synthesis* **1999**, 1145-1148; b) S. A. Shahzad, C. Venin, T. Wirth, *Eur. J. Org. Chem*. **2010**, 3465-3472; c) X.-D. Fei, Z.-Y. Ge, T. Tang, Y.-M. Zhu, S.-J. Ji, *J. Org. Chem*. **2012**, *77*, 10321-10328; d) M. R. Kumar, F. M. Irudayanathan, J. H. Moon, S. Lee, *Adv. Synth. Catal*. **2013**, *355*, 3221-3230; e) H. Liu, Y. Yang, J. Wu, X.-N. Wang, J. Chang, *Chem.Commun*. **2016**, *52*, 6801-6804; f) G. Liu, G. Kuang, X. Zhang, N. Lu, Y. Fu, Y. Peng, Y. Zhou, *Org. Lett*. **2019**, *21*, 3043-3047; From 2-alkynylbenzoates: g) M. Uchiyama, H. Ozawa, K. Takuma, Y. Matsumoto, M. Yonehara, K. Hiroya, T. Sakamoto, *Org. Lett*. **2006**, *8*, 5517-5520; h) M. Hellal, J.-J. Bourguignon, F. J.-J. Bihel, *Tetrahedron Letters* **2008**, *49*, 62-65; i) T. Yoshikawa, M. Shindo, *Org. Lett*. **2009**, *11*, 5378-5381; j) J. Francos, V. Cadierno, *Catalysts* **2017**, *7*, 328; k) Y. Kita, T. Yata, Y. Nishimoto, K. Chibac, M. Yasuda, *Chem. Sci.* **2018**, *9*, 6041-6052; l) J. Gianni, V. Pirovano, G Abbiati, *Org. Biomol. Chem.* **2018**, *16*, 3213-3219; m) F. Curti, M. Tiecco, V. Pirovano, R. Germani, A Caselli, E. Rossi, G. Abbiati, *Eur. J. Org. Chem*. **2019**, 1904-1914.

[3] a) T. Yao, R. C. Larock, *Tetrahedron Lett.* **2002,** *43*, 7401-7404; b) T. Yao, R. C. Larock, *J. Org. Chem*. **2003**, *68*, 5936-5942; c) R. Rossi, A. Carpita, F. Bellina, P. Stabilea, L. Mannina, *Tetrahedron* **2003**, *59*, 2067-2081; d) Y. Wang, J. D. Burton, *J. Org. Chem.* **2006**, *71*, 3859-3862; e) M. Peuchmaur, V. Lisowski, C. Gandreuil, L. T. Maillard, J. Martinez, J.-F. Hernandez, *J. Org. Chem*. **2009**, *74*, 4158-4165; f) J. H. Park, S. V. Bhilare, S. W. Youn, *Org. Lett.* **2011**, *13*, 2228-2231; g) A. Speranca, B. Godoi, S. Pinton, D. F. Back, P. H. Menezes, G. Zeni, *J. Org. Chem*. **2011**, *76*, 6789-6797; h) Z. Li, J. Hong, L. Weng, X. Zhou, *Tetrahedron* **2012**, *68*, 1552-1559; i) P. Saikia, S. Gogoi, *Adv. Synth. Catal*. **2018**, *360*, 2063-2075; j) J S. S. Neto, D. F. Back, G. Zeni, *Eur. J. Org. Chem*. **2015**, 1583-1589.

[4] a) K. Komeyama, K. Takahashi, K. Takaki, *Org. Lett.* **2008**, *10*, 5119-5122; b) Y. Soltani, L. C. Wilkins, R. L. Melen, *Angew. Chem. Int. Ed*. **2017**, *56*, 11995-11999; c) M. A. Amin, J. S. Johnson, S. A. Blum, *Organometallics* **2014**, *33*, 5448-5456; d) Y. Shi, K. E. Roth, S. D. Ramgren, S. A. Blum, *J. Am. Chem. Soc*. **2009**, *131*, 18022-18023; e) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. D. B. Becker, M. Rudolph, C. Scholz, F. Rominger, *Adv. Synth. Catal*. **2012**, *354*, 133-147; f) Y. Soltani, L. C.

Wilkins, R. L. Melen, *Synlett* **2018**, *29*, 1-7; g) P. Zhao, D. Chen, G. Song, K. Han, X. Li, *J. Org. Chem.* **2012**, *77*, 1579-1584; h) H. Wang, X. Han, X. Lu, *Tetrahedron* **2013,** *69*, 8626-8631; i) P.-P. Tian, S.-H. Cai, Q.-J. Liang, X.-Y. Zhou, Y.-H. Xu, T.-P. Loh, *Org. Lett.* **2015**, *17*, 1636-1639; j) R. S. Pathare, S. Sharma, K. Gopal, D. M. Sawant, R. T. Pardasani, *Tetrahedron Lett.* **2017**, *58*, 1387-1389; k) T. Ahmad, S.-Q Qiu, Y.-H. Xu, T.-P. Loh, *J. Org. Chem*. **2018**, *83*, 13414-13426; l) S.-Q. Qiu, T. Ahmad, Y.-H. Xu, T.-P. Loh, *J. Org. Chem.* **2019**, *84*, 6729-6736; m) S. W. Youna, H. J. Yoo, *Adv. Synth. Catal.* **2017**, *359*, 2176-2183; n) J. Zhang, X. Han, X. Lu, *J. Org. Chem*. **2016**, *81*, 3423-3429.

[5] a) S. Sadhukhan, B. Baire, *Chem. Eur. J*, **2019**, *25*, 9816–9820; b) S. Sadhukhan, B. Baire, *Chem. Select*, **2019**, *4*, 3376-3380; c) S. Gandhi, B. Baire, *Chem. Select*, **2018**, *3*, 4490-4494; d) P. Tharra and B. Baire, *Org. Lett.*, **2018**, *20*, 1118-1121; e) S. Sadhukhan, B. Baire, *Adv. Synth. Catal.*, **2018**, *360*, 298-304; f) S. Sadhukhan, B. Baire, *Chem. Select* **2017**, *2*, 8500-8503; g) P. Tharra, B. Baire, *Chem. Eur. J.*, **2017**, *23*, 2014-2017; h) S. Gandhi, P. Tharra, B. Baire, *Chem. Select* **2017**, *2*, 1058-1062; i) P. Tharra, B. Baire, *Chem. Comm.* **2016**, *52*, 14290-14293; j) P. Tharra, B. Baire, *Chem. Commun*. **2016**, *52*, 12147-12150.

[6] Gandhi, S.; Baire, B. *J. Org. Chem.* **2019**, *84*, 3904-3918.

[7] S. V. Nadkarni, J. M. Nagarkar, *Green Chem. Lett. Rev*. **2011**, *4*, 121-126.

[8] Crystallographic data information for the isocoumarin **6** has been deposited with the Cambridge Crystallographic Data Centre with CCDC1920455 number. Further details are given in supporting information file.

[9] When standard reaction conditions are employed, all the alcohols resulted in an inseparable mixture of simple isocoumarin **10** and the coupled products **9m-p** along with variable amounts of unreacted starting material **4**; please see SI, Table S1 for details)

[10] a) S. E. Duran, L. J. Donnelly, E. B. Mclean, B. M. Hockin, A. M. Z. Slawin, J. E. Taylor, *Chem. Eur. J.* **2019**, *25*, 3950-3956; b) P. K. Sahoo, S. S. Gawali, C. Gunanathan, *ACS Omega* **2018**, *3*, 124-136.

[11] Y. Li, G. Li, Q. Ding, *Eur. J. Org. Chem.* **2014**, 5017–5022.

[12] Crystallographic data information for the phthalide-pyran **27a*Z*** has been deposited with the Cambridge Crystallographic Data Centre with CCDC1920456 number. Further details are given in supporting information file.

[13] Crystallographic data information for the phthalide-quinoline **27r*E*** has been deposited with the Cambridge Crystallographic Data Centre with CCDC1920457 number. Further details are given in supporting information file.

10.1002/adsc.202000313

FULL PAPER

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