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Regiocontrolled Intramolecular Cyclizations of Carboxylic Acids to Carbon–Carbon Triple Bonds Promoted by Acid or Base Catalyst

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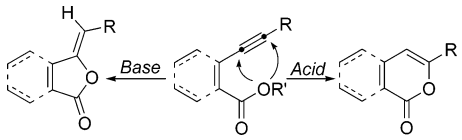
ABSTRACT



We systematically investigated, for the first time, the relationship between regioselectivity and acid/base effects in the cyclization reactions between carboxylic acids and carbon–carbon triple bonds. We found novel acid- and base-promoted cyclizations to selectively give isocoumarin or pyran-2(2*H*)-one and phthalide or furan-2(5*H*)-one skeletons, respectively, and established a catalytic version of regioselective heterocyclic ring synthesis. Density functional theory calculations and application to a short route to thunberginol A were also described.

The carbon−carbon triple bond is among the most important functional groups in organic chemistry and has been used in organic synthesis, mechanistic studies, and in the synthesis of functionalized materials.[1] Recently, significant progress has been made in heterocyclic ring construction via the intramolecular annulation of carboxylic acids, amides, alcohols, and amines to a variety of carbon−carbon triple bonds.[1]

Intramolecular cyclization of enynecarboxylic acid systems **1** can afford both pyran-2(2*H*)-one (**2**) and furan-2(5*H*)-one (**3**) derivatives (Figure 1).[2] As each of these skeletons represents an important class of naturally occurring lactones with a wide range of biological and pharmacological activities, much attention has been focused on their selective syntheses.[2−4] However, a general procedure for achieving

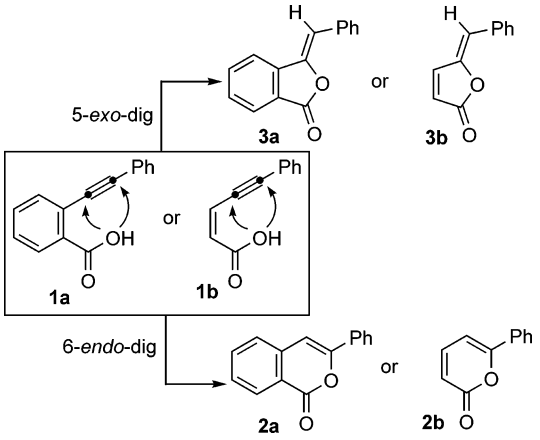


Figure 1. Phthalide (5-*exo*) vs isocoumarin (6-*endo*) cyclization.

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(1) Book: Hart, H. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons Ltd.: New York, 1994.

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selective synthesis from an enynecarboxylic acid system **1** has not been available.[5] Furthermore, Baldwin's rule predicts that both 5-*exo*-*dig* and 6-*endo*-*dig* cyclizations are favorable, making selective synthesis difficult in practice.[6,7] Herein, we describe a novel, selective cyclization from an enynecarboxylic acid system, based on asymmetrical activation of the carbon−carbon triple bond by either acid or base catalyst and its application to the synthesis of thunberginol A (**4**).

In order to achieve regioselective activations of the carbon−carbon triple bonds of 2-(2-phenylethynyl)benzoic acids (**1a**), we systematically examined the relationship between regioselectivity and solvent acidity or basicity (Table 1). As the simple heating of **1a** at reflux in toluene (neutral solvent) did not effect thermal cyclization, we next examined the reactions of **1a** in the presence of a variety of acid catalysts. Cyclization was not observed at all in acids as weak as acetic acid, while stronger acids such as CF_3COOH, 97% H_2SO_4, and CF_3SO_3H (TFSA) catalyzed the 6-*endo* cyclization selectively to give 3-phenylisocoumarin (**2a**)[8] in good to excellent yields. In sulfuric acid, the yield of **2a** was relatively low, presumably due to sulfonylation. In TFSA, the yield of **2a** was almost quantitative. In contrast, nitrogen-containing, basic catalysts, such as pyridine and triethylamine, induced the opposite regioselectivity, giving (*Z*)-3-(1-benzylidene)phthalide (**3a**) selectively,[9] together with a small amount of **2a**. More strongly basic catalysts, such as sodium ethoxide and sodium hydride, proved ineffective (entries 8−10). Thus, the selective syntheses of isocoumarin and phthalide skeletons from 2-(2-phenylethynyl)benzoic acid (**1a**) were achieved through the use of simple acid and base catalysts, respectively.

Table 1. Phthalide (5-*exo*) vs Isocoumarin (6-*endo*) Cyclization

entry	solvent& conditions			Yield (%) **2a** + **3a**	ratio **2a** : **3a**
1	CF_3SO_3H	*acidic*	r.t., 12 h	96	**99** : <1
2	97% H_2SO_4		r.t., 12 h	63	**99** : <1
3	CF_3COOH		r.t., 12 h	88	**99** : <1
4	CH_3COOH		r.t., 12 h	0	-
5	Toluene	*neutral*	r.t., (reflux) 12 h	0 (0)	- (-)
6	Pyridine		reflux, 12 h	96	3 : **97**
7	Et_3N		reflux, 12 h	85	2 : **98**
8	NaOEt, EtOH		reflux, 12 h	0	-
9	NaH, Toluene		reflux, 12 h	0	-
10	NaH, DMSO	*basic*	60 °C, 12 h	0	-

We next focused our attention on the role of the catalyst in promoting the different cyclization modes of **1**. It appears that protonation or deprotonation of the carboxylic acid (**1**) is critical in determining the resulting regioselectivity. Plausible mechanisms for alternative intramolecular cyclizations of **1**, leading to either phthalide (5-*exo*) or isocoumarin (6-*endo*) skeletons are depicted in Figure 2. In the presence of strong acid catalysts, the carbonyl group of **1** is protonated, as would be expected from the basicity of the acid carbonyl oxygen atoms (cf. pK_{BH+} value of benzoic acid = −7.18 to −7.38).[10] Thus, the electronic bias on both carbons of the triple bond favors Michael-type (6-*endo*) cyclization. In the presence of basic catalysts, the carboxylate anion can be generated via deprotonation of the carboxylic acid, providing the initial intermediate for cyclization. These intuitions are in good agreement with the DFT-calculated value (Figures 2 and 3).

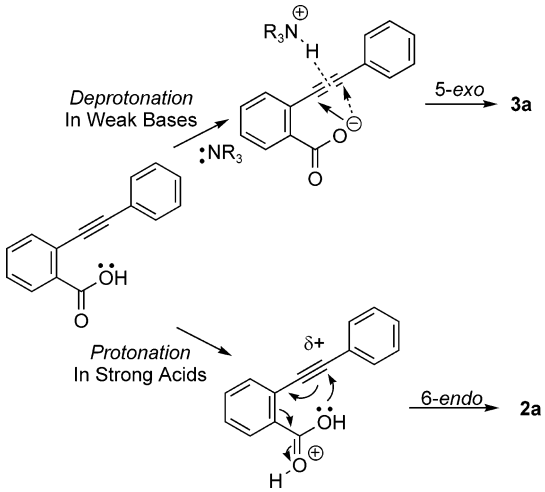


Figure 2. Possible mechanisms for phthalide (5-*exo*) vs isocoumarin (6-*endo*) cyclization.

Because of the protonation−deprotonation equilibria, the acid or base catalysts should be regenerated at the final step.

(2) (a) Letsinger, R. L.; Oftedahl, E. N.; Nazy, J. R. *J. Am. Chem. Soc.* **1965**, *87*, 742−749. (b) Sakamoto, T.; An-naka, M.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2754−2759. (c) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145−1148. (d) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255−1261. (e) Anastasia, L.; Xu, C.; Negishi, E.-i. *Tetrahedron Lett.* **2002**, *43*, 5673−5676.

(3) 3-Substituted isocoumarin skeleton: (a) Barry, R. D. *Chem. Rev.* **1964**, *64*, 229−260. (b) Turner, W. B. *Fungal Metabolites*; Academic Press: London, 1971; Chapter 5. (c) Hill, R. A. In *Progress in the Chemistry of Organic Natural Products*; Wien-Springer-Verlag: New York, 1986; Vol. 49. (d) Bovicelli, P.; Lupattelli, P.; Crescenzi, B.; Sanetti, A.; Bernini, R. *Tetrahedron* **1999**, *55*, 14719−14728. (e) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533−2545. (f) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936−5942. (g) Cherry, K.; Parrain, J. L.; Thibonnet, J.; Duchene, A.; Abarbri, M. *J. Org. Chem.* **2005**, *70*, 6669−6675. (h) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778−4783. (i) Woon, E. C. Y.; Dhami, A.; Mahon, M. F.; Threadgill, M. D. *Tetrahedron* **2006**, *62*, 4829−4837 and references cited therein.

(4) 3-Alkylidenephtalide skeleton: Rossi, R.; Bellina, F.; Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett.* **2000**, *41*, 5281−5286 and references cited therein.

(5) Only one successful example of the silver salt-catalyzed cyclization of 2-(1-pentynyl)benzoic acid has been reported: Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, *41*, 2587−2599.

(6) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. (b) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476−482.

(7) We have reported some cyclization reactions which cannot be explained in terms of Baldwin's rule; see: (a) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733−8734. (b) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934−4946.

(8) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711−3716.

(9) Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, *60*, 561−568.

(10) Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223−403 and references cited therein.

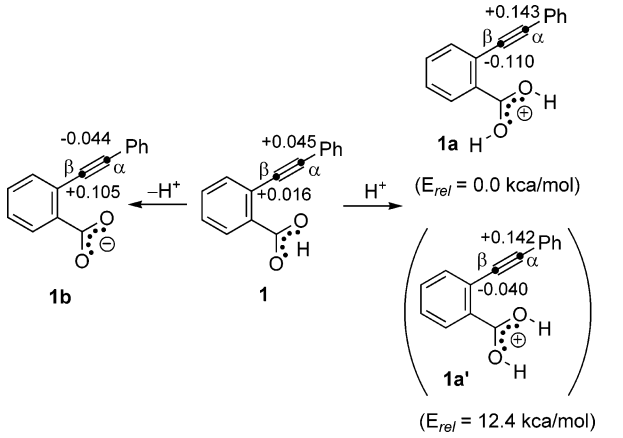


Figure 3. Natural population analysis (B3LYP/6-31+G*).

Indeed, both cyclizations proceeded in refluxing toluene in the presence of a catalytic amount of strong acid or weak base, with high selectivities and in high yields (Table 2). In these selective catalytic cyclizations, CF_3SO_3H and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) proved the most effective acid and base catalysts, respectively.

Table 2. Acid- or Base-Catalyzed Phthalide vs Isocoumarin Cyclization

entry	conditions	yield (%) **2a** + **3a**	ratio **2a**:**3a**
1	CF_3SO_3H (1 mol %), toluene, reflux, 12 h	100	**97**:3
2	$TsOH{\cdot}H_2O$ (10 mol %), toluene, reflux, 24 h	100	**92**:8
3	Et_3N (100 mol %), toluene, reflux, 12 h	99	4:**96**
4	DMAP (0.5 mol %), toluene, reflux, 24 h	98	2:**98**

Once the conditions for the selective cyclization of 2-phenylethynylbenzoic acid had been optimized, we sought to apply this strategy to the selective synthesis of pyran-2(2*H*)-one and furan-2(5*H*)-one skeletons (Table 3).[11,12] In the case of (*Z*)-5-phenyl-2-penten-4-ynoic acid (**1b**), the 5-*exo* cyclization proceeded preferentially under reflux in toluene. The same cyclization was also found to proceed selectively in the weakly basic solvent pyridine, without any additive or catalyst. Next, in hopes of obtaining the pyran-2(2*H*)-one skeleton preferentially, **1b** was stirred in a strongly acidic solvent, such as CF_3COOH or CF_3SO_3H; under these conditions, the desired 6-*endo* cyclization proceeded selectively to give **2b**. Moreover, it was found that the 5-*exo* and 6-*endo* cyclizations of **1b** can also be controlled through the appropriate choice of catalyst. A catalytic amount of acid also favors 6-*endo* cyclization, albeit less selectively. Although the reason for this reduction in selectivity is not clear at present, the possibility the competition between acid catalyzed (**1b** → **2b**) and uncatalyzed reaction (**1b** → **3b**) as entry 4 in Table 3 cannot be ruled out.

Table 3. Acid- or Base-Promoted Furan-2(5*H*)-one vs Pyran-2(2*H*)-one Cyclization

entry	solvent (reagent)	*T* (°C)	time (h)	yield (%) **2b** + **3b**	ratio **2b**:**3b**
1	CF_3SO_3H	rt	13	62	**99**:<1
2	CF_3COOH	rt	71	65	**99**:<1
3	toluene	65	12	0	
4	toluene	reflux	72	89	1>:**99**
5	pyridine	reflux	13	89	1>:**99**
6	toluene (50 mol % CF_3SO_3H)	65	6.5	88	68:32
7	toluene (10 mol % DMAP)	65	3.5	93	1>:**9**

Under basic conditions, a catalytic amount of base promotes high selectivity for 5-*exo* cyclization.

With the reaction conditions thus optimized, we next focused our efforts on applying the new methodology to the synthesis of the natural product. Thunberginols were isolated from *Hydrangea bacrophylla* SERINGE var. *thunbergii* MAKINO by Yoshikawa in 1992 and known for having unique biological activities, e.g., antiallergic and antimicrobial activities.[13] Among several syntheses[14] of thunberginol A (**4**), Rossi reported the construction of the pyran-2(2*H*)-one system via two successive reactions, namely, cyclization of the acetylenic ester mediated by iodine, followed by reductive removal of the iodine atom catalyzed by palladium complex.[14d] We speculated that the cyclization and deprotection steps could be carried out simultaneously under our optimized acidic conditions. Thus, we undertook the synthesis of thunberginol A, using commercially available **5** and **8** as starting materials (Scheme 1).

The bis-phenolic hydroxyl group of 3,4-dihydroxybenzaldehyde (**5**) was protected as the bis-*tert*-butyldimethylsilyl ether under standard conditions, and aldehyde **6** was converted to **7** by the Corey−Fuchs method.[15] In a separate reaction, the phenolic hydroxyl group and the carboxylate

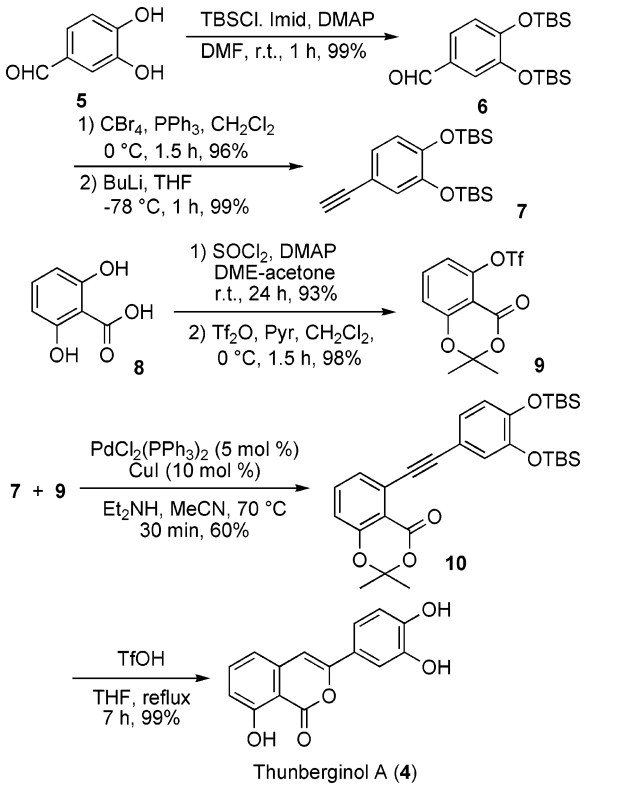
(11) Furan-2(5*H*)-ones: (a) Tsuboi, S.; Wada, H.; Mimura, S.; Takeda, A. *Chem. Lett.* **1987**, 937−938. (b) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135−156.

(12) Pyran-2(2*H*)-one: (a) Tominaga, Y.; Ushirogochi, A.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 1557−1567. (b) Barrero, A. F.; Oltra, J. E.; Herrador, M. M.; Sanchez, J. E.; Quilez, J. T.; Rojas, F. J.; Reyes, J. F. *Tetrahedron* **1993**, *49*, 141−150. (c) Biagetti, M.; Bellina, F.; Carpita, A.; Viel, S.; Mannina, L.; Rossi, R. *Eur. J. Org. Chem.* **2002**, 1063−1076.

(13) (a) Yoshikawa, M.; Uchida, E.; Chatani, N.; Murakami, N.; Yamahara, J. *J. Chem. Pharm. Bull.* **1992**, *40*, 3121−3123. (b) Yoshikawa, M.; Uchida, E.; Naitoh, Y.; Inoue, K.; Matsuda, H.; Shimoda, H.; Yamahara, J.; Murakami, N. *J. Chem. Pharm. Bull.* **1994**, *42*, 2225−2230. (c) Yoshikawa, M.; Matsuda, H.; Shimoda, H.; Shimada, H.; Harada, E.; Naitoh, Y.; Miki, A.; Yamahara, J.; Murakami, N. *J. Chem. Pharm. Bull.* **1996**, *44*, 1440−1447. (d) Matsuda, H.; Shimoda, H.; Yamahara, J.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 215−220.

(14) (a) Ohta, S.; Kamata, Y.; Inagaki, T.; Masuda, Y.; Yamamoto, S.; Yamashita, M.; Kawasaki, I. *Chem. Pharm. Bull.* **1993**, *41*, 1188−1190. (b) Yoshikawa, M.; Harada, E.; Yagi, N.; Okuno, Y.; Muraoka, O.; Aoyama, H.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 721−723. (c) Yoshikawa, M.; Shimada, H.; Yagi, N.; Murakami, N.; Shimoda, H.; Yamahara, J.; Matsuda, H. *Chem. Pharm. Bull.* **1996**, *44*, 1890−1898. (d) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023−5038.

Scheme 1. Synthesis of Thunberginol A



of 2,6-dihydroxybenzoic acid (**8**) were protected as the acetal, and the resulting hydroxyl group was converted to the triflate **9** in good overall yield. The Sonogashira coupling reaction between **7** and **9** was conducted in the presence of $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), and Et_2NH (1.5 equiv) in MeCN to afford **10** in 60% yield. Finally, the cyclization and deprotection steps were accomplished in the same reaction with TfOH (1.0 equiv) in refluxing THF to furnish thunberginol A (**4**) (99%).

In conclusion, we report dramatic acid/base effects on the mode of cyclization between carboxylic acids and carbon−carbon triple bonds. Specifically, the selective syntheses of phthalide/isocoumarin and furan-2(5*H*)-one/pyran-2(2*H*)-one skeletons were achieved, with the selectivity depending upon whether a strong acid or weak base was employed as the catalyst. Further studies to delineate the scope and limitations of the present methodology are underway, together with investigations into the application of this methodology in the synthesis of natural products and functional materials.

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Supporting Information Available: Experimental procedures and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769−3772.