Advanced Synthesis & Catalysis

Accepted Article

Title: Rapid access to indeno[1,2-c]quinolines via Brønsted-Acid Catalyzed Cascade Reaction

Authors: Sivasenthilkumar Boominathan

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700190

Link to VoR: http://dx.doi.org/10.1002/adsc.201700190

10.1002/adsc.201700190

COMMUNICATION

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

Rapid access to indeno[1,2-*c*]quinolines via Brønsted-Acid Catalyzed Cascade Reaction

Siva Senthil Kumar Boominathan,[a] and Jeh-Jeng Wang[a,b]*

[a] Department of Medicinal & Applied Chemistry, Kaohsiung Medical University, No. 100, Shiquan 1st Rd, Kaohsiung 807, Taiwan.
Fax: (+886)-7-312-5339; phone: (+886)-7-312-1101; E-mail: jjwang@kmu.edu.tw
[b] Department of Medical Research, Kaohsiung Medical University Hospital, No.100, Tzyou 1st Rd, Kaohsiung 807, Taiwan.

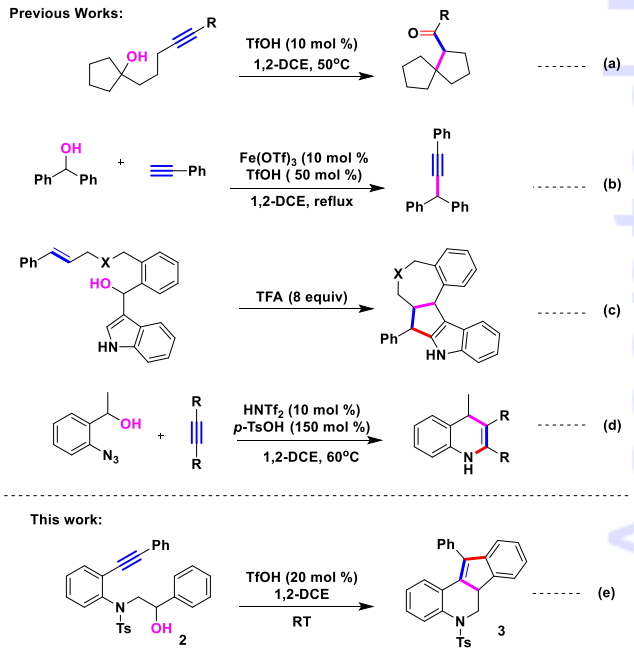
Received: ((will be filled in by the editorial staff))

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. A Brønsted acid catalyzed annulation strategy has been developed to construct indeno[1,2-*c*]quinolines. This tandem synthetic method proceeds through a sequential electrophilic addition followed by a Friedel-Crafts type reaction. A variety of tetracyclic compounds were obtained in moderate to high yields under mild reaction conditions in a short time.

Keywords: Indeno[1,2-c]quinolines, Brønsted acid catalysis, cascade reaction, Polycyclic heterocycles, Alkynes

In recent years, Brønsted acid catalysis has emerged as a simple and powerful synthetic strategy that is complimentary to Lewis acid catalysis to access C-C, C-N, and C-O bond forming reactions.[1] Although Brønsted acids have long been employed in organic synthesis, they have rather limited applications, such as hydrolysis, ester formation, and C-O cleavage reactions. The economic attractiveness and mild nature of these catalysts have made their use significant in recent decades. In general, Brønsted acid catalyzed reactions proceed via the activation of carbonyl, imine, alkyne, alkene, and hydroxy groups to beget reactive electrophiles, which then trigger nucleophilic addition reactions. The use of Brønsted acid promoted alcohol pro-electrophiles trapped by alkynes could be a judicious choice to construct polycyclic skeletons, but to our knowledge, few studies have made use of this strategy. In 2009, Yamamoto et. al. reported an elegant approach to preparing spirocycles from alkynyl tertiary alcohols using a catalytic amount of trifluoromethanesulfonic acid (TfOH) (**Scheme 1**; **eq. a**).[2a] Shortly after that, Jiao and co-workers reported a direct C(sp)−C(sp^3) coupling reaction in the presence of $Fe(OTf)_3$ and TfOH (**eq. b**).[2b] A trifluoroacetic acid (TFA) promoted cascade cyclization yielding fused-polycyclic cyclopenta[*b*]indoles was developed by Hamada in 2013 (**eq. c**).[2c] Very recently, Niggemann disclosed a convenient method to quinoline frameworks from carboamination of unactivated alkynes promoted by bis(trifluoromethanesulfonyl)imide ($(Tf)_2NH$) and *p*-toluenesulfonic acid (*p*-TsOH) (**eq. d**).[2d] Encouraged by these pioneering studies and driven by our continuing efforts to develop new synthetic methods from *β*-keto sulfonamides,[3] here we have conceptualized a synthetic strategy using *β*-hydroxy sulfonamides as potential precursors, with the aid of a Brønsted acid, to synthesize indeno[1,2-*c*]quinolines (**Scheme 1**; **eq. e**).



Scheme 1. Functionalization of alcohols with alkynes/alkenes under Brønsted acid catalysis.

Cascade chemical reactions in organic synthesis have intensely inspired the scientific community in-

10.1002/adsc.201700190

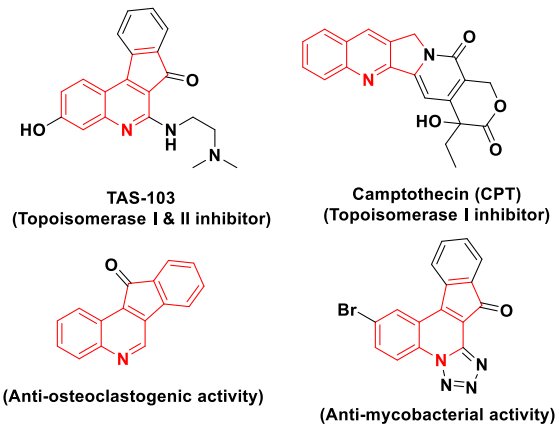
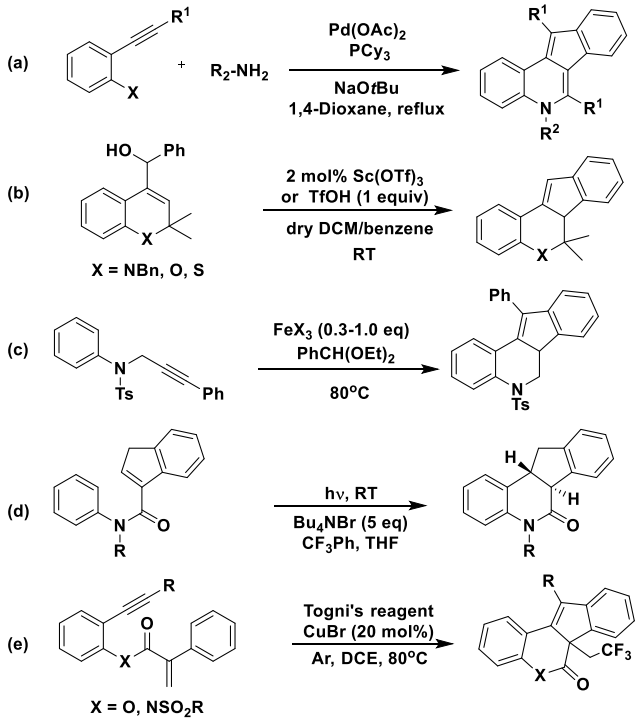
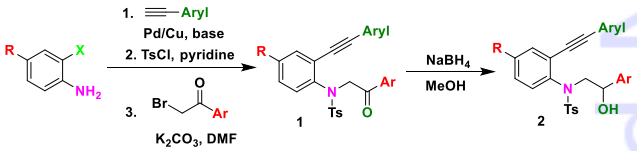


Figure 1. Bioactive compounds containing indenoquinolines.



Scheme 2: Previous approaches to indene fused quinolines.

-recent years, as demonstrated by the vast number of research articles and reviews published on the topic.[4] These reactions provide convenient and straightforward routes to achieving structural complexity from simple precursors. Among the ubiquitous nitrogen-containing heterocycles, quinoline fused frameworks hold a special place due to their prevalence in naturally occurring compounds, pharmaceuticals, and materials. Evidently, indene-fused quinolines derivatives have appear in several bioactive molecules and have proven applications such as topoisomerase I/II inhibitors,[5] anti-osteoclastogenic activators,[6] anti-cancer properties,[7] and anti-mycobacterials (**Figure 1**).[8] The available methods to prepare these compounds (**Scheme 2**) are very limited, which has encouraged us to develop a practical route to indene-fused quinoline analogues. In 2011, Wu et. al. reported a palladium catalyzed domino type reaction of alkynyl aryl halides with amines to prepare 5*H*-indeno[1,2-c]quinolines (**Scheme 2**, eq. a).[9a] A nazarov type electrocyclization approach towards these tetracyclic compounds via $Sc(OTf)_3$ or TfOH reported by panda in 2011 (**eq. b**).[9b] An iron salts mediated tandem carboarylation/cyclization of propargylanilines with diethyl benzaldehyde acetals to indeno[2,1-*c*]quinolines was developed by Yu et. al. in 2014 (**eq. c**).[9c] Yamamoto and coworkers were developed a TBABr promoted photocyclization of acrylanilides to these tetracyclic compounds (**eq. d**).[9d] Recently, Wang et. al. developed a copper-catalyzed 1,7-enyne trifluoromethylation/bicyclization reaction with Togni's reagent to indene and dihydroquinolinone fused heterocycles (**eq. e**).[9e] Despite their great efforts, the available methods to prepare these compounds are very limited and suffering from certain limitations like harsh reaction conditions, need of pre-constructed quinoline/indene starting materials, limited substitution pattern, transition-metal catalysts, and poor reaction yields. These limitations and significance of these scaffolds have encouraged us to develop a practical route to indene-fused quinoline analogues. The present method exemplifies the efficient construction of these scaffolds using catalytic amount of TfOH under mild reaction conditions in short time (**Scheme 1**; **eq. e**).



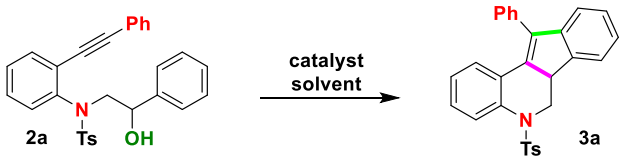
Scheme 3. Synthetic Scheme for Starting material

Initially, the desired precursors were synthesized from commercially available starting materials as shown in **Scheme 3**. The substituted 2-iodo anilines undergo Sonogashira coupling with respective aryl alkynes, followed by sulfonylation and subsequent alkylation by corresponding α-bromoaryl ketones to give β-keto sulfonamide derivatives (**1**) in a stepwise manner in quantitative yields.[3c] Next, the keto group of compound **1** is reduced in the presence of sodium borohydride to afford β-hydroxy sulfonamides (**2**), which were used in the final step without further purification (See SI for details).

We commenced our study by investigating the reaction of compound **2a** with various acid catalysts, and the results are assembled in **Table 1**. The reaction was first carried out with 10 mol % of TfOH in 1,2-DCE at RT (**Table 1**; entry 1). Gratifyingly, the expected tetracyclic compound **3a** was obtained in 72% yield, and X-ray crystallographic analysis confirmed the structure (**Figure 2**).[10] We then screened this tandem reaction with different acid catalysts such as Tf_2NH, TFA, *p*-TsOH, and $BF_3{\cdot}OEt_2$ (entries 2-5),

and among them, only Tf_2NH responded well to this reaction. However, we settled on TfOH as the choice of a catalyst, because it was significantly less costly than Tf_2NH. A short screening of solvents, such as dichloromethane, chloroform, nitromethane, and toluene (entries 6-9), resulted in significantly lower product yield. Thus, we chose 1,2-DCE as the optimal solvent. No reaction took place in the absence of acid catalyst (entry 10). Increasing the amount of catalyst from 10 to 20 mol % led to a further improvement in the reaction yield from 72 to 84%, and we fixed this entry as the optimal set of reaction conditions (**Table 1**, entry 11).

Table 1. Optimization Studies[a]

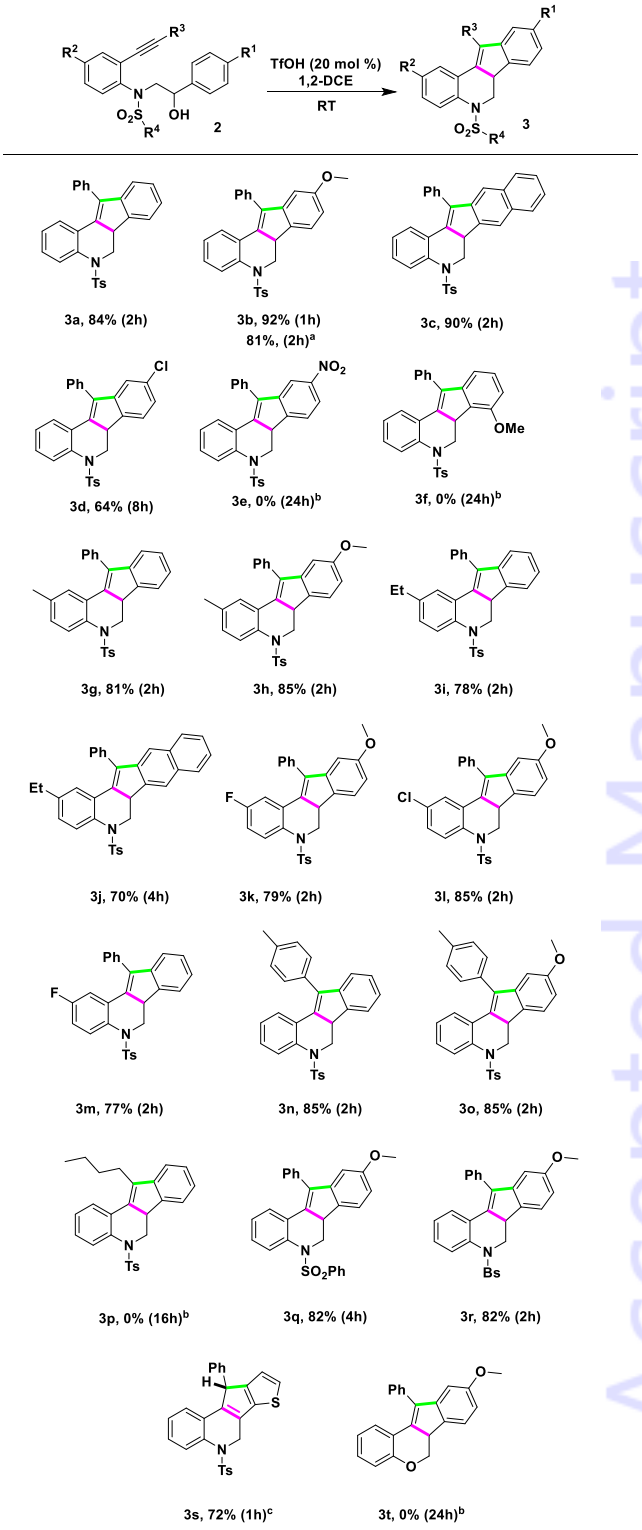


entry	catalyst	solvent	temp(°C)/ time (h)	yield[e] (%)
1	TfOH	1,2-DCE	RT/2	72
2	Tf2NH	1,2-DCE	RT/2	74
3	TFA	1,2-DCE	RT/16	15
4[b]	p-TsOH	1,2-DCE	RT-80/16	Trace
5[b]	$BF_3{\cdot}OEt_2$	1,2-DCE	RT-80/16	Trace
6	TfOH	DCM	RT/4	70
7[c]	TfOH	$CHCl_3$	RT-60/4	55
8b	TfOH	CH_3NO_2	RT-80/8	35
9	TfOH	toluene	RT-80/12	Trace
10	-	1,2-DCE	RT-80/16	0
11[d]	TfOH	1,2-DCE	RT/2	84

[a]General reaction conditions: Compound **2a** (0.25 mmol), catalyst (10 mol %), solvent (0.05 M). [b]No reaction occurred at RT; thus, the reaction was heated to 80 °C. [c]No reaction occurred at RT; thus, the reaction was heated to 60 °C. [d]20 mol % catalyst was used. [e]Isolated yields.

The scope and limitations of this methodology were investigated under the optimized reaction conditions and summarized in **Scheme 4**. First, R^1 on the phenyl ring was replaced with methoxy, naphthyl, and chloro (**3a-d**) groups, which led to the desired annulatedproducts in good yields. Notably, the phenyl ring appended with electron donating group reacted very well in short time with excellent yields (**3b**). Conversely, the substrates bearing electron withdrawing groups such as a nitro group (**3e**) failed to cyclize even at elevated temperature, possibly due to lessened stability of the in situ generated benzylic cation (vide infra). Similarly, the R^1 at the C-2 position (**3f**) also turned into a complex reaction mixture that could not be identified by NMR analysis. Next, the fluoro, and chloro substituents (**3g-m**) were smoothly transformed into the respective products with high yields. Furthermore, the molecules with the phenyl group at the R^3 position changed to a *p*-tolyl group (**3n-**

Scheme 4. Substrate Scope



General reaction conditions: Compound **2** (0.25 mmol), and catalyst (20 mol %) in a solvent (0.05 M) were stirred at RT for the mentioned time given in parenthesis. [a]Reaction was performed at 1.5 gram scale. [b]No reaction occurred at RT; thus, the reaction was heated to 60 °C. [c]Reactions were conducted at 0-5 °C for 60 min; longer reaction times decreased the reaction yield.

o) underwent the tandem reaction with greater yields; nevertheless, an alkyl group at the R^3 position was unsuccessful (**3p**). In addition, replacing the tosyl group with phenyl sulfonyl (**3q**) and brosyl (Bs) groups (**3r**) gave the expected tetracyclic compounds. It is noteworthy that the thiophene appended tetracyclic product was obtained in a short time with high yield (**3s**), but the double bond present in the cyclopentane ring was isomerized. Crystal studies unambiguously confirmed the structure of **3s** (**Figure 2**).[9] The use of sulfonamides was essential to set off the domino process, and its replacement with oxygen to prepare indeno[1,2-*c*]chromenes was ineffective (**3t**).

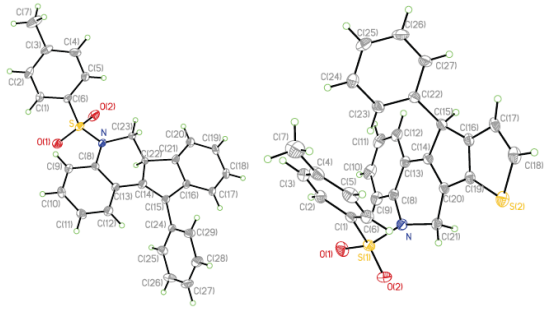
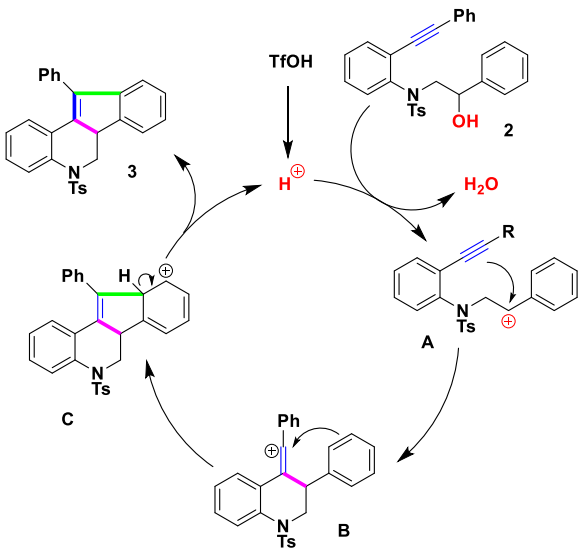


Figure 2. ORTEP diagram of Compound **3a** and **3s**

Based on the observed results and the literature,[2,11] a tentative reaction mechanism for this transformation has been proposed in **Scheme 5**. First, the alcohol is ionized by the aid of TfOH to give the putative benzylic cation (A), which, after being further attacked by a nucleophilic alkyne, gives a vinyl carbocation (B). A subsequent Friedel-Crafts type reaction between the aryl group and vinyl cation provides the indeno[1,2-*c*]quinolines, and the expelled catalyst participates in the next cycle.



Scheme 5. Proposed Reaction Mechanism

In summary, we have reported a simple and straightforward route to indeno[1,2-*c*]quinolines via Brønsted acid catalysis. Advantageously, water is the only by-product, making this protocol environmentally benign and atom-efficient. The experimental simplicity, scalability, short reaction time, simple precursors, and cascade reaction sequence make this route highly intriguing from a synthetic perspective, and it may find useful applications in medicinal chemistry.

Experimental Section

General procedure for synthesis of compound **3a-s**:

To a stirred solution of compound **2a** (0.25 mmol) in 1,2-DCE (0.05 M) was added with catalytic amount of TfOH (20 mol%) and stirred at RT for mentioned time and temperature. After reaction completed (monitored by TLC), reaction mass partitioned between water and DCM. The combined organic layer was washed with sat. NH_4Cl solution, dried on sodium sulphate and evaporated under vacuum gives crude. Then, the crude was purified by flash column chromatography on silica gel with suitable ratio of Hexane/EtOAc to afford the corresponding product (**3a**).

Acknowledgements

The authors gratefully acknowledge funding from the Ministry of Science and Technology (MOST), Taiwan, and the Centre for Research Resources and Development of Kaohsiung Medical University for 400 MHz NMR analyses.

References

[1] a) T. Akiyama, K. Mori, *Chem. Rev.* **2015**, *115*, 9277−9306; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744−5758; c) C. H. Cheon, H. Yamamoto, *Chem. Commun.* **2011**, *47*, 3043–3056; d) H. Yamamoto, K. Ishihara, *Acid catalysis in modern organic synthesis;* Wiley-VCH: Weinheim, 2008; e) C. Theunissen, B. Métayer, N. Henry, G. Compain, J. Marrot, A. Martin-Mingot, S. Thibaudeau, G. Evano, *J. Am. Chem. Soc.* **2014**, *136*, 12528–12531.

[2] a) T. Jin, M. Himuro, Y. Yamamoto, *Angew. Chem., Int. Ed.* **2009**, *48*, 5893−5896; b) S. –K. Xiang, L. –H. Zhang, N. Jiao, *Chem. Commun.* **2009**, *45*, 6487−6489; c) T. Yokosaka, H. Nakayama, T. Nemoto, Y. Hamada, *Org. Lett.* **2013**, *15*, 2978–2981. d) T. Stopka, M. Niggemann, *Chem. Commun.* **2016**, *52*, 5761-5764.

[3] a) S. S. K. Boominathan, W. –P. Hu, G. C. Senadi, J. –J. Wang, *Adv. Synth. Catal.* **2013**, *355*, 3570-3574; b) S. S. K. Boominathan, W. –P. Hu, G. C. Senadi, J. K. Vandavasi, J. –J. Wang, *Chem. Commun.* **2014**, *50*, 6726-6728; c) S. S. K. Boominathan, G. C. Senadi, J. K. Vandavasi, J. –Y. F. Chen, J. –J. Wang, *Chem.-Eur. J.* **2015**, *21*, 3193-3197; d) G. C. Senadi, W. –P. Hu, S. S. K. Boominathan, J. –J. Wang, *Chem.-Eur. J.*, **2015**, *21*, 998-1003; e) S. S. K. Boominathan, R. –J. Hou, W. –P. Hu, P. –J. Huang, J. –J. Wang, *Adv. Synth. Catal.* **2016**, *358*, 2984-2989.

[4] a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis;* Wiley-VCH: Weinheim, 2006; b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed*. **2006**, *45*, 7134–7186; c) K. C. Nicolaou, J. S. Chena, *Chem. Soc. Rev*. **2009**, *38*, 2993-3009; d) X. Zeng, *Chem. Rev*. **2013**, *113*, 6864−6900; e) R. Ardkhean, D. F. J. Caputo, S. Morrow, H. Shi, Y. Xiong, E. A. Anderson, *Chem. Soc. Rev*. **2016**, *45*, 1557-1569.

[5] a) C. –H. Tseng, C. –C. Tzeng, C. –L. Yang, P. –J. Lu, Y. –P. Liu, H. –L. Chen, C. –Y. Chen, C. -N. Yang, Y. -L. Chen, *Mol. Divers*, **2013**, *17*, 781–799; b) C. –H. Tseng, C. –C. Tzeng, C. –L. Yang, P. –J. Lu, H. –L. Chen, H. –Y. Li, Y. –C. Chuang, C. –N. Yang, Y. –L. Chen, *J. Med. Chem*. **2010**, *53*, 6164–6179; c) C. –H. Tseng, Y. –L. Chen, P. –J. Lu, C. –N. Yang, C. –C. Tzeng, *Bioorg. Med. Chem*. **2008**, *15*, 3153–3162; d) A. Ryckebusch, D. Garcin, A. Lansiaux, J. –F. Goossens, B. Baldeyrou, R. Houssin, C. Bailly, J. –P. Henichar, *J. Med. Chem*. **2008**, *51*, 3617-3629.

[6] C. –H. Tseng, R. –W. Lin, Y. –L. Chen, G. –J. Wang, M. L. Ho, C. –C. Tzeng, *J. Med. Chem*. **2011**, *54*, 3103–3107.

[7] T. Utsugi, K. Aoyagi, T. Asao, S. Okazaki, Y. Aoyagi, M. Sano, K. Wierzba, Y. Yamada, *Jpn. J. Cancer Res*. **1997**, *88*, 992–1002.

[8] a) R. S. Upadhayaya, P. D. Shinde, A. Y. Sayyed, S. A. Kadam, A. N. Bawane, A. Poddar, O. Plashkevych, A. Foldesic, J. Chattopadhyaya, *Org. Biomol. Chem.* **2010**, *8*, 5661–5673; b) R. S. Upadhayaya, S. V. Lahore, A. Y. Sayyed, S. S. Dixit, P. D. Shinde, J. Chattopadhyaya, *Org. Biomol. Chem.* **2010**, *8*, 2180–2197.

[9] a) Y. Luo, X. Pan, J. Wu, *Org. Lett.* **2011**, *13*, 1150–1153; b) R. Singh, G. Panda, *Org. Biomol. Chem*., **2011**, *9*, 4782-4790; c) Q. Yang, T. Xu, Z. Yu, *Org. Lett*. **2014**, *16*, 6310−6313; d) S. Yamada, M. Okuda, N. Yamamoto, *Tetrahedron Lett*., **2015**, *56*, 2098–2101; e) Q. Wang, H. Song, Y. Liu, H. Song, Q. Wang, *Adv. Synth. Catal*. **2016**, *358*, 3435-3442.

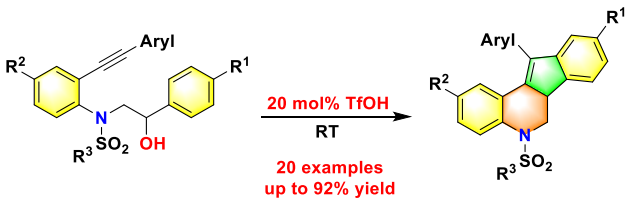
[10] a) CCDC 1517832 (**3a**), and CCDC 1517833 (**3s**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] R. Naredla, D. A. Klumpp, *Chem. Rev*. **2013**, *113*, 6905−6948.

10.1002/adsc.201700190

COMMUNICATION

Rapid access to indeno[1,2-*c*]quinolines via Brønsted-Acid Catalyzed Cascade Reaction



Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Siva Senthil Kumar Boominathan and Jeh-Jeng Wang*