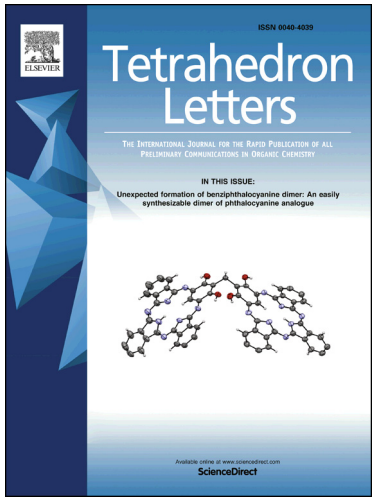

Regioselective Annulation of Propargyl Alcohols with Ambident-Enols: A Ca(II)-Catalyzed trisubstituted Benzochromene Synthesis

Srinivasarao Yaragorla, Abhishek Pareek, Ravikrishna Dada

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Graphical Abstract`

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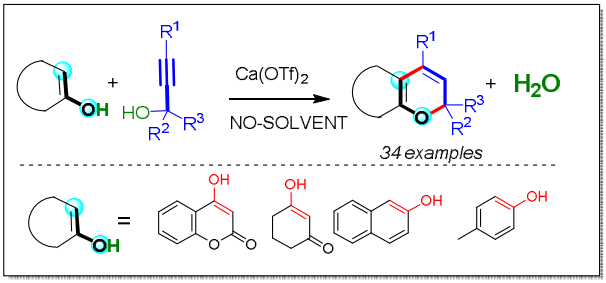

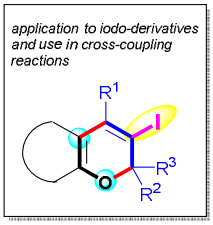

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Regioselective Annulation of Propargyl Alcohols with Ambident-Enols: A Ca(II)-Catalyzed trisubstituted Benzochromene Synthesis

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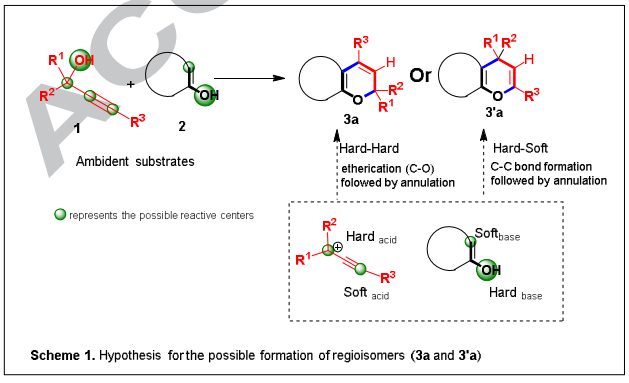
ABSTRACT

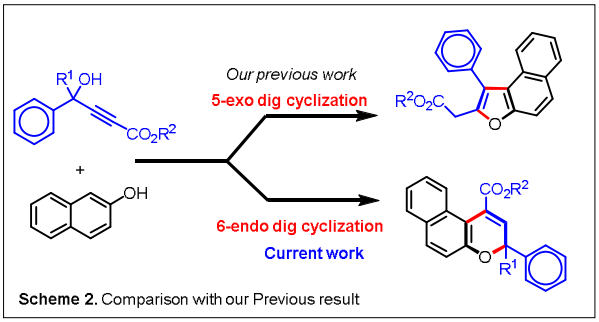
Highly regioselective, 6-endo cyclization between propargyl alcohols and ambident enols such as naphthols, 4-hydroxy coumarin, cyclohexane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione is described using $Ca(OTf)_2$ under solvent free conditions. The reaction proceeds through a cascade annulation which involves an etherification, Claisen type rearrangement, allene formation and endocyclization. Further, we extended this method to the synthesis of iodo-derivative and demonstrated the reactivity in cross-coupling reactions.

Ambident nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms can be drawn in which two or more atoms bear an unshared pair of electrons. Therefore ambident nucleophiles may attack in two or more different ways to give different products.[1] Enols are one of the most important types of ambident nucleophiles, used extensively as reagents in organic synthesis.[2] Enols can react through hard oxygen or soft carbon with the ambident substrates based on the conditions. As depicted in the Scheme 1, the ambident enol (**2**) can react with the ambident propargyl alcohol (**1**) to give two possible regioisomeric benzopyrans **3a** or **3'a**. Indeed, propargyl alcohol reacts with the Lewis acid to produce the propargyl cation (3^o-carbocation) which is a hard acid, then ambident enol reacts with this hard acid (3^o-carbocation) through its hard base (oxygen,-OH) to furnish more stable regioisomer **3a** through a hard-hard interactions. Alternatively, ambident enol may react with this hard acid ((3^o-carbocation) through its soft base (carbon) to furnish less stable **3'a** through a hard-soft interactions.



Scheme 1. Hypothesis for the possible formation of regioisomers (**3a** and **3'a**)

Therefore, it can be understood that, under thermodynamic conditions **3a** can be the major or exclusive product. Owing to the biological importance[3] and natural abundance[4] of the benzeochromene derivatives (pyran derivatives) several synthetic methods were reported[5,6]. In continuation of our research aimed to develop the regioselective methods for the synthesis of privileged molecules using propargyl alcohols as synthons,[7] here in we are reporting a highly facile, regioselective, solvent free reaction between propargyl alcohols and enols.



Scheme 2. Comparison with our Previous result

We commenced our investigation by using easily available propargyl alcohol **1a** and 2-naphthol **2a** in the presence of 10 mol% of $Ca(OTf)_2$, 10 mol% of Bu_4NPF_6 in 1,2-dichloroethane at rt (25 ^oC). To our delight product **3a** was formed in 50% after 5 h (single product), however, there was no significant progress in the reaction till 12 h (Table 1, entry 1). When refluxed in DCE at 90 ^oC, the reaction yielded **3a** in 74% after 5 h (entry 2). The yield of **3a** was raised to 81% after 90 minutes, when a mixture of **1a**, **2a** and 10 mol% of $Ca(OTf)_2/Bu_4NPF_6$ was heated to 110 ^oC, in the absence of solvent (entry 3). Attempts to minimize the catalyst loadings were moderately successful to get the maximum yield of **3a** (entries 4, 5). However, in the absence of the additive,

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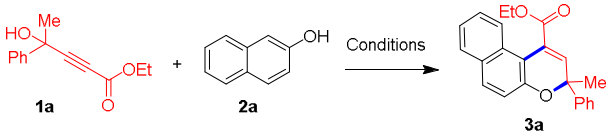
the reaction yielded only 20% of **3a** (entry 6), therefore the presence of additive is necessary, so that a ligand metathesis takes place between $Ca(OTf)_2$ and Bu_4NPF_6 to furnish $Ca[(OTf)(PF_6)]$ with increased Lewis acidity. Other additives such as, KPF_6, NH_4BF_4, and Bu_4NF gave moderate yields with $Ca(OTf)_2$ (entries 7-9). Metal catalysts, such as $Mg(OTf)_2$ and $FeCl_3$ were employed, but moderate yield of **3a** was obtained (entries 10,11). The reaction did not occur in water (entry 12) and another protic-solvent, ethanol gave only 20% of the product and rest of the propargyl alcohol converted into corresponding ether (entry 13). The reaction gave 45% product in an aprotic nonpolar solvent, toluene (entry 14).

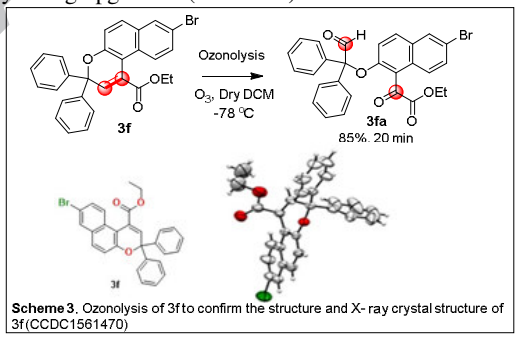
Table 1. Optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Conditions[b]	Yield (%)[c]
1	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	1,2-DCE, rt, 5 h	50
2	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	1,2-DCE, 90 °C, 5 h	74
3	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Neat, 110 °C, 1.5 h	81
4[d]	$Ca(OTf)_2/Bu_4NPF_6$ (05/10)	Neat, 110 °C, 1.5 h	81
5	$Ca(OTf)_2/Bu_4NPF_6$ (05/05)	Neat, 110 °C, 5 h	75
6	$Ca(OTf)_2$ (10)	Neat, 110 °C, 10 h	20
7	$Ca(OTf)_2/KPF_6$ (10/10)	Neat, 110 °C, 3 h	65
8	$Ca(OTf)_2/NH_4BF_4$ (10/10)	Neat, 110 °C, 6 h	55
9	$Ca(OTf)_2/Bu_4NF$ (10/10)	Neat, 110 °C, 3 h	62
10	$Mg(OTf)_2/Bu_4NPF_6$ (10/10)	Neat, 110 °C, 6 h	61
11	$FeCl_3$ (10)	Neat, 110 °C, 10 h	53
12	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Water, 110 °C, 12 h	nr
13	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Ethanol, 90 °C, 10 h	20[e]
14	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Toluene, 110 °C, 6 h	45

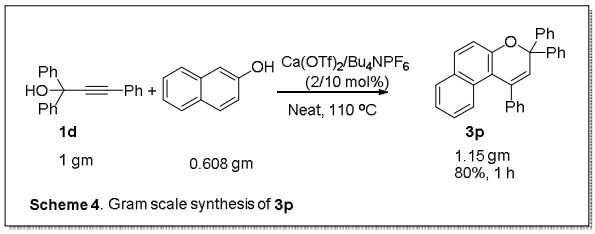
[a]1 equiv of **1a** and 1.2 equib of **2a** were used. [b]Oil bath temperature. [c]Isolated yields. [d]Optimum conditions. [e]remaining compound was found as propargyl ether. rt=room temp (25 °C)

Though our hypothesis in the Scheme 1 suggests the possible formation of two regioisomeric benzopyrans, the rationale suggested (HSAB theory) a thermodynamically stable single isomer and the experimental result also confirmed the single regioisomer (Table 1). To confirm the structure of the product, we subjected the compound **3f** to ozonlysis (O_3, DCM, -78 °C) and obtained the product **3fa** in 85% yield (Scheme 3). Further the structure of compound **3f** was unambiguously endorsed by X-ray crystallograpgic data (Scheme 3).



Scheme 3. Ozonolysis of 3f to confirm the structure and X- ray crystal structure of 3f(CCDC1561470)

Having the optimal conditions in hand, we next examined the generality of our regioselective transformation as showed in Table 2. Propargyl alcohol **1a** (ethyl 4-hydroxy-4-phenylpent-2-ynoate) was treated with a variety of phenolic compounds under standard conditions and gratifyingly the products **3a-3d** were isolated as single isomers in excellent yields. Propargyl alcohol **1b** (ethyl 4-hydroxy-4,4-diphenylbut-2-ynoate) was also reacting well with the phenols bearing (Br, Cl, Me) different substitutions and yielded the products **3e-3h** (Table 2). Products **3i-3l** were synthesized in excellent yields from propargyl alcohol **1c** (methyl 4-hydroxy-4,4-diphenylbut-2-ynoate) with phenolic compounds. After the successful demonstration of scope of ambident phenols in the annulation reaction, next we moved to the check the reactivity of another ambident enol, 4-hydroxycoumarin and synthesized the products **3m**, **3n** and **3o** by treating 4-hydroxy coumarin with **1a**, **1b** and **1c** respectively. So far the scope of propargyl alcohols bearing ester group was demonstrated hence we further planned to replace the ester group with aryl moiety. For example **1d** (1,1,3-triphenylprop-2-yn-1-ol) was treated with naphthols in presence of 2 mol% $Ca(OTf)_2$/10 mol% Bu_4NPF_6 at 110 °C under neat conditions gave the naphthopyrans **3p-3r** in good yields. Similarly, other triaryl propargyl alcohols (Table 2) reacted with naphthols and 4-hydroxy coumarin and yielded the pyran derivatives **3s-3x** in good yields. 1,3-diketones, such as 5,5-dimethylcyclohexane-1,3-dione and cyclohexane-1,3-dione exists in keto-enol tautomersim and hence considered as ambident enols and treated with propargyl alcohols to get the pyrans **3y** and **3z** in good yields. 1-(phenylethynyl)cyclohexan-1-ol gave the spirocyclic pyrans **3aa-3ac** with naphthols. Another spiro compound **3ad** was synthesized from 4-hydroxy coumarin and 9-(phenylethynyl)-9H-fluoren-9-ol. 2-methyl-4-phenylbut-3-yn-2-ol gave the pyran derivatives **3ae-3ag** in excellent yields. Finally, 2-methyl-4-(trimethylsilyl)but-3-yn-2-ol was treated with 4-methoxynaphthalen-1-ol under standard conditions and obtained 74% of **3ah**, which resembles the Lapachenole natural product (depicted in the box, Table 2).

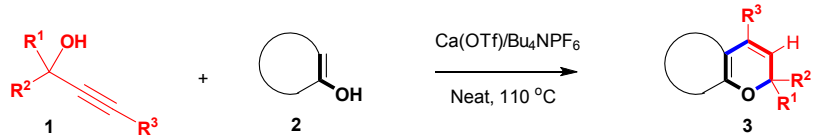


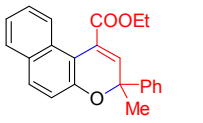
Scheme 4. Gram scale synthesis of **3p**

The scalability of this solvent free method for the synthesis of 1,3,3-triphenyl-3H-benzo[f]chromene **3p** (1150 mg, 80% yield) from 2-naphthol and propargyl alcohol **1d** was demonstrated in the Scheme 4.

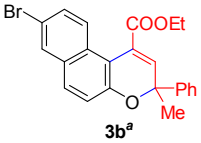
After the successful development of a regioselective method for the solvent free synthesis of benzo/naphthochromens, we planned the synthesis of 2-iodo-derivatives.[5c] Therefore **1d** and **2a** were treated with 2 mol% $Ca(OTf)_2$/10 mol% Bu_4NPF_6, iodine (2 equiv) in toluene at rt for 1.5 h and found that the reaction yielded a mixture (4:1) of **4a** and **3p** in 88% yield (Scheme 5). Encouraged by these observations, we then decided to see the reactivity of this 2-iodo pyran derivative in cross-coupling reactions. Since **4a** and **3p** were formed as an inseparable mixture, we treated the mixture with ethyl acrylate under Heck conditions[8,7d] ($Pd(OAc)_2$, Bu_4NBr, K_2CO_3, DMF, 80 °C, 22 h), to obtain **5** in 66% yield (the product **3p** was also separated). The iodide mixture (**4a+3p**) was also subjected to the Sonogashira cross coupling reaction[9,7d] with acetylene ($Pd(OAc)_2$, DABCO, CH_3CN, rt, 12 h) and obtained the product **6** in 61% yield (Scheme 5).

Table 2. Substrate scope of Calcium catalyzed regioselective annulation of propargyl alcohols with ambident enols

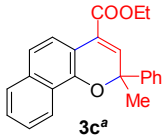




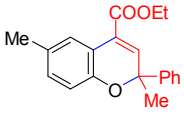
3a[a]
81%, 1.5 h



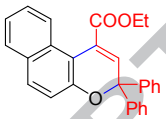
3b[a]
76%, 3 h



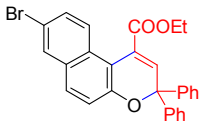
3c[a]
86%, 2 h



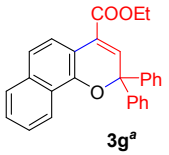
3d[a]
75%, 4 h



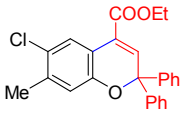
3e[a]
72 % , 4.5 h



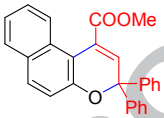
3f[a] (CCDC:1561470)
63%, 6 h



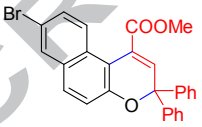
3g[a]
86%, 2 h



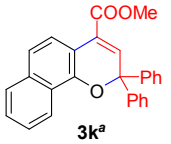
3h[a]
75%, 4 h



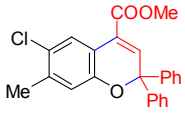
3i[a]
81%, 2 h



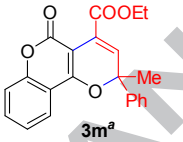
3j[a]
77%, 2 h



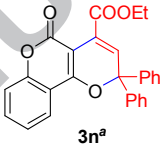
3k[a]
72%, 3 h



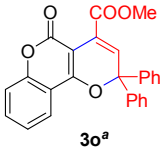
3l[a]
79%,3.5 h



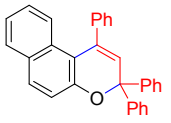
3m[a]
76%, 3 h



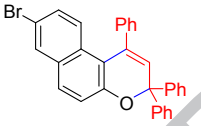
3n[a]
69%, 5 h



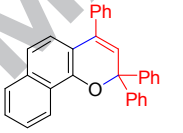
3o[a]
81%, 3 h



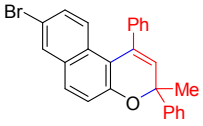
3p[b]
88%, 30 min



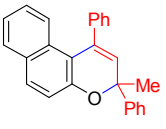
3q[b]
87%, 45 min



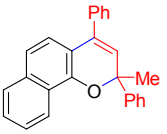
3r[b]
81%, 1h



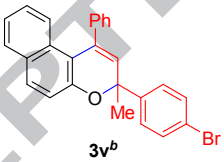
3s[b]
84%, 45 min



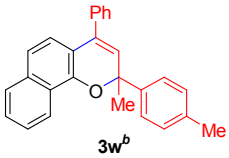
3t[b]
76%, 45 min



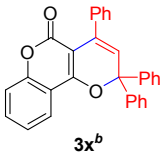
3u[b]
77%, 1 h



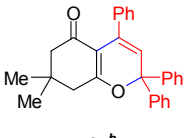
3v[b]
82%, 50 min



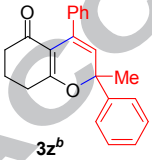
3w[b]
70%, 2h



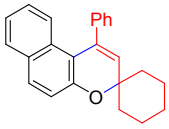
3x[b]
75%, 2.5 h



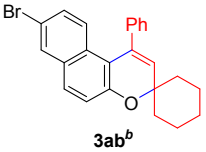
3y[b]
77%, 2 h



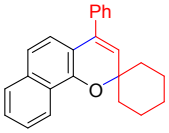
3z[b]
75%, 1.5 h



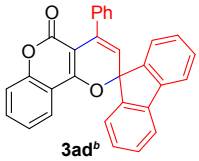
3aa[b]
86%, 50 min



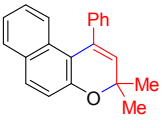
3ab[b]
84%, 45 min



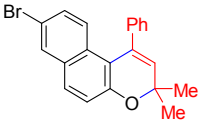
3ac[b]
76%, 1 h



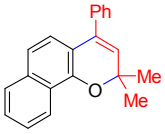
3ad[b]
77%, 2 h



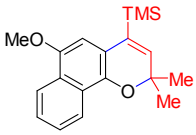
3ae[b]
91%, 30 min



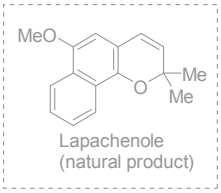
3af[b]
83%, 50 min



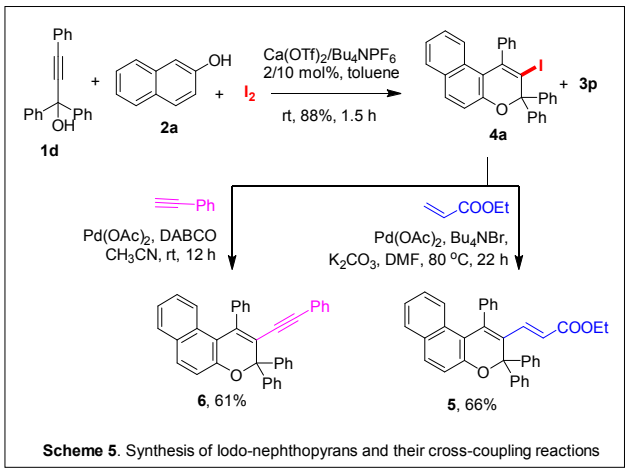
3ag[b]
89%, 40 min



3ah[b]
74%, 3 h

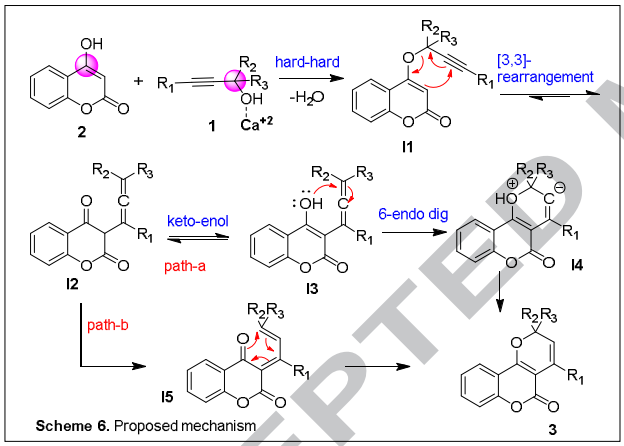


Reaction conditions: [a]1eq. of **1**, 1.2 eq. of **2**, 5 mol% of $Ca(OTf)_2$ and 10 mol% Bu_4NPF_6 were heated at 110 °C (oil bath temperature) for specified time; [b].1eq. of **1**, 1.2 eq. of **2**, 2 mol% of $Ca(OTf)_2$ and 10 mol% Bu_4NPF_6 were heated at 110 °C (oil bath temperature) for specified time;



Scheme 5. Synthesis of Iodo-nephthopyrans and their cross-coupling reactions

We proposed the possible reaction mechanism for the synthesis of **3** from **1** and **2** in the Scheme 6. Initially the oxophilic calcium promotes the formation of vinyl-propargyl ether **I1** from **2** and **1** (hard-hard), which then undergoes a thermodynamic-[3,3] rearrangement[5e] to furnish the allene **I2**. Allene **I2** can readily form the enol **I3** (path-a), which then undergo a regioselective, 6-endo cyclization to yield the desired product **3**. Alternatively (path-b), allene **I2** can rearrange to a diene and then cyclize to give the product **3**.



Scheme 6. Proposed mechanism

In summary, we developed a regioselective annulation reaction between propargyl alcohols and ambident enols using calcium triflate as the sustainable lewis acid catalyst, under solvent free conditions. Through this approach, we introduced the carboxylate derivatives of benzochromenes as new chemical entities. Ozonolysis and X-ray data supported the structure of the products. We extended this method for the synthesis of iodo-pyrans, further the synthetic utlity is demonstrated through cross coupling reactions.

All compounds were fully characterized by ^{1}H, ^{13}C NMR, IR, Mass, melting point and X ray data as required.[10]

Acknowledgements

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10. Refer to the supporting information for complete details of experimental procedures, spectral data and copies of the spectra.

Highlights of the Work

Regioselective Annulation of Propargyl Alcohols with Ambident-Enols: A Ca(II)-Catalyzed trisubstituted Benzochromene Synthesis

- **Highly regioselective Synthesis**
- **Involves a Cascade Process of etherification, [3,3] rearrangement, allene formation and endocyclization**
- **Solvent-Free Synthesis**
- **Large Substrate Scope with High Yields**
- **Extended to iodo-derivatives and demonstrated the cross-couplings**