irradiation, that result in a significant reduction in the yield and/or make difficult the later modifications of these compounds. In fact, chalcone derivatives can be used as starting materials for producing other classes of compounds such as flavonoids or pyrazoles.

Phase transfer catalysis, which is considered as a reliable strategy for the asymmetric synthesis of organic compounds in simple experimental conditions, mild reaction conditions, and for large-scale preparations, has been used to the modify chalcone derivatives through condensation of intermediate compounds, as well as epoxidation or Michael addition of chalcone derivatives (Ooi T and Marouka K, 2007; Song G and Ahn B, 1994; Li J and Liu X, 2008; Rao G et al., 2009).

The synthesis and/or further modification of chalcone derivatives that contain at least a phenyl ring with substituent groups on adjacent carbon atoms of the ring can be inefficient due to steric hindrance. Alternative synthetic strategies for producing such chalcone derivatives, in particular by either S-alkylation or O-alkylation, have been described in the literature cited above and elsewhere (WO 05/005369, WO 04/056727). However, the need for novel methods allowing the efficient production of chalcone derivatives that have multiple substitutions, and in particular on adjacent carbon atoms of a phenyl ring, is still clear and urgent.

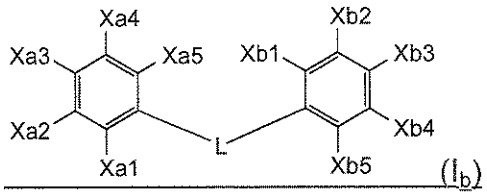
SUMMARY ~~OF INVENTION~~

The present disclosure~~invention~~ provides highly efficient methods for producing chalcone derivatives with multiple substitutions on a phenyl ring. Intermediate chalcone derivatives are modified by Phase Transfer Catalysis (PTC) for introducing a substituted alkyl group that is provided by a sulfonic acid derivative on a phenyl ring already containing substituent groups on one or two carbon atoms adjacent to the carbon atom where the substituent group is being introduced.

The disclosed methods ~~of the invention~~ allow producing efficiently, by either S-alkylation or O-alkylation, chalcones derivatives that are characterized for their biological activities that

are intermediate compounds for producing molecules having such activities, and/or that can be used for generating libraries of compounds to be screened by means of *in vitro* and/or *in vivo* assays and establishing structure-activity relationships.

In one aspect, there is provided a method for preparing a compound of following General Formula (I_b):



(I_b)

wherein:

X_{a1}, X_{a2}, X_{a3}, X_{a4}, and X_{a5}, identical or different, are a hydrogen atom, a halogen atom, a R_a or G_a-R_a group;

R_a is an alkyl, an alkenyl, a cycloalkyl, an aryl, an alkyloxy, an alkylthio, or a heterocyclic group, said group can be substituted or not, or R_a is a protecting group linked to the phenyl ring by an oxygen atom or sulfur atom;

L is a CO- R_L or R_L-CO group;

X_{b1}, X_{b2}, X_{b3}, X_{b4}, and X_{b5} are substituent groups, wherein one of them is a R'_b-G_b-R_c or G_b-R_c group, and at least one of other substituent groups adjacent to said R'_b-G_b-R_c or a G_b-R_c group is a halogen atom or a R''_b group, the remaining groups being independently hydrogen atoms, halogen atoms or R''_b groups;

R''_b is an alkyl, an alkenyl, a cycloalkyl, an aryl, an alkyloxy, an alkylthio, or a heterocyclic group, said group can be substituted or not, or R''_b is a protecting group linked to the phenyl ring by an oxygen atom or sulfur atom;

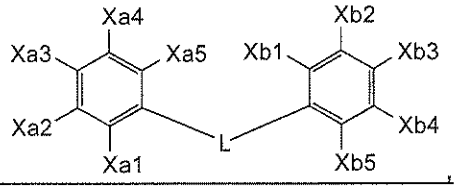
R'_b is an alkyl, an alkenyl, a cycloalkyl, an aryl, an alkyloxy, an alkylthio, or a heterocyclic group, said group can be substituted or not;

R_L is an unsubstituted or substituted alkyl or alkenyl group;

G_a and G_b, identical or different, are an oxygen atom or sulfur atom;

R_c is an alkyl group substituted by at least a $-COOR_d$ group, wherein R_d is an unsubstituted alkyl, alkenyl, aryl, cycloalkyl, or heterocyclic group;

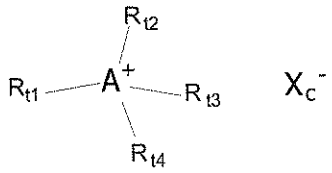
said method comprising the following steps:

a) Obtaining the compound of General Formula (I_a) 

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in which X_{a1}, X_{a2}, X_{a3}, X_{a4}, X_{a5}, L, R_a, R'_b, R''_b, R_L, G_a, and G_b group are defined as for General Formula (I_b); and X_{b1}, X_{b2}, X_{b3}, X_{b4}, and X_{b5} are substituent groups wherein one of them is a R'_b-G_b-H or G_b-H group, and at least one of the substituent groups adjacent to said R'_b-G_b-H or G_b-H group is a halogen or a R''_b group, the remaining groups being independently hydrogen atoms, halogen atoms or R''_b groups;

b) contacting the compound of General Formula (I_a) with a sulfonic acid derivative of General Formula (II) R_s-SO_2-O-R_c, in a biphasic organic solvent / water medium, and in presence of a compound of General Formula (III):



(III),

in which:

- R_s, R_{t1}, R_{t2}, R_{t3}, and R_{t4}, identical or different, are unsubstituted alkyl groups;
- A is a nitrogen or phosphorus atom ;
- X_c is an halogen, HSO_4, or H_2PO_4; and
- R_c is defined as for General Formula (I_b).

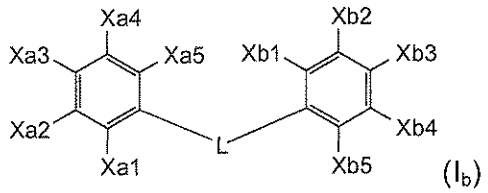
Further embodiment~~objects~~ of the present disclosure~~invention~~ are provided in the Detailed Description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for producing compounds that contain two phenyl groups linked to each other, wherein one of said phenyl groups is substituted in at least two (and preferably at least three) positions, a conformation that characterize compounds having medical interest but that can make the later modification of one of such positions poorly efficient due to the steric hindrance. This effect occurs when the size of groups within a molecule prevents chemical reactions in a specific position, limiting the possibilities of generating variants of natural or synthetic compounds having biological and pharmaceutical activities, such as chalcone derivatives for which the literature shows the importance of having multiple substituents on a single phenyl ring.

The invention provides methods for producing chalcone derivatives of General Formula (I_b) by using appropriate reactants and conditions for applying Phase Transfer Catalysis (PTC), in particular by either S-alkylation or O-alkylation. These reactants and conditions are not disclosed in the prior art as being applicable for the synthesis of chalcone derivatives of General Formula (I_b). Moreover, as shown in the Examples, a series of 1,3-diphenylprop-2-en-1-ones has been successfully produced according to the Invention with improved yields and purity.

In the main embodiment, the present invention provides a method for preparing a compound of following General Formula (I_b):



(I_b)