

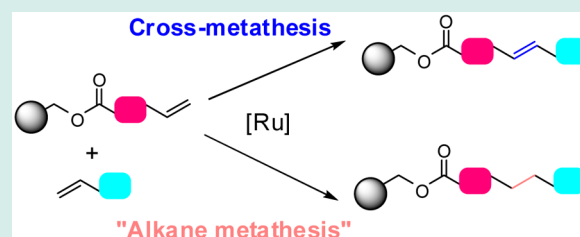
Solid-Supported Cross-Metathesis and a Formal Alkane Metathesis for the Generation of Biologically Relevant Molecules

Luciana Méndez and Ernesto G. Mata*

Instituto de Química Rosario (CONICET—UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, 2000 Rosario, Argentina

Supporting Information

ABSTRACT: Solid-phase synthetic strategies toward the generation of libraries of biologically relevant molecules were developed using olefin cross-metathesis as a key step. It is remarkably the formal alkane metathesis based on a one-pot, microwave-assisted, ruthenium-catalyzed cross-metathesis and reduction to obtain $C_{sp^3}-C_{sp^3}$ linkages.



KEYWORDS: olefin metathesis, solid-phase organic synthesis, chalcones, β -phenylpropiophenone derivatives, microwave heating

The application of metal-catalyzed cross-coupling reactions to solid-phase organic synthesis has increased substantially in the past decade.¹ This has been caused by the emergence of new and more efficient catalysts and the inherent advantages of solid-supported chemistry, including an increase in selectivity.² Since the desired product is immobilized on a resin, undesirable side reactions that take place in solution are easily washed away by a simple filtration. In addition, spatial separation between the reactive sites (pseudo high dilution conditions)³ make intramolecular macrocyclization a suitable reaction that could be carried out efficiently on solid-phase rather than in solution. An extra benefit of the solid-phase synthesis is obtained when it is applied to cross-coupling reactions: unwanted homodimeric products can be either easily removed or not formed at all. The nonimmobilized substrate can be added in excess in order to complete the reaction since the corresponding homodimer remains in solution and can be eliminated by a simple filtration. Similarly, homodimerization of the immobilized substrate is a less favorable process due to the isolation between the reactive sites.⁴

On the other hand, studies related to the synthesis and properties of small molecules remains an essential strategy for identifying lead compounds for treatment of diseases.⁵ There is a growing interest in the development of new ways to obtain such small molecules not only for their use in traditional drug discovery but also for the use in dissecting protein–protein interactions and for understanding signaling pathways.⁶ Thus, one of the methodologies for a rapid and efficient construction of diversity-based small molecules is parallel solid-phase synthesis which, after an initial use in the preparation of peptides, is now extensively employed in the preparation of biologically interesting molecules including heterocycles and natural product scaffolds,⁷ becoming an important tool to improve the efficiency of drug discovery.⁸

Regarding the likelihood of identifying new active structures in drug discovery, recent analyses have demonstrated that current compound collections exhibit a low incidence of sp^3 carbon atoms in their molecules, and the tendency is even more marked in the last 15 years.⁹ A high level of carbon bond saturation, defined the fraction sp^3 (F_{sp^3}), indicates a more three-dimensional, less “flat” structure.¹⁰ Many recent studies, supported by computational analysis, have suggested that larger F_{sp^3} values can improve the possibility of finding new drug candidates.¹¹

Among structures that show a wide spectrum of beneficial biological activities, chalcones (**1**) occupy an important place (Figure 1). They are versatile synthetic and natural scaffolds found in antibacterial,¹² antifungal,¹³ antituberculosis,¹⁴ anti-inflammatory,¹⁵ and especially, in antitumor agents, that is,

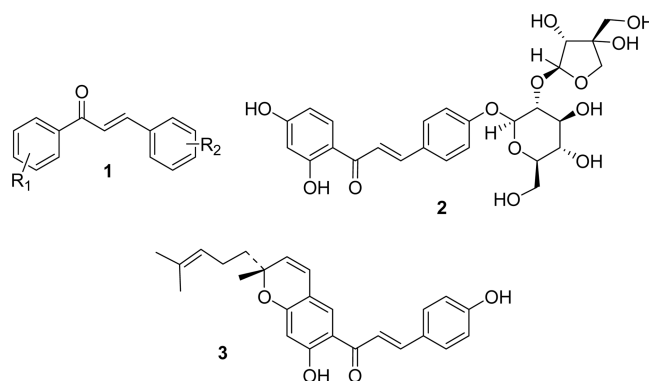


Figure 1. Some chalcone derivatives of biological interest.

Received: November 13, 2014

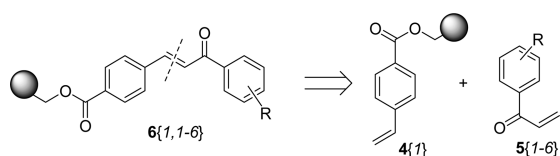
Revised: January 3, 2015

Published: January 8, 2015

isoliquiritin apioside (**2**) and isolespeol (**3**) (Figure 1).¹⁶ All previous solid-phase synthesis of chalcones were based on aldol condensation between ketones and aldehydes, usually employing strong bases.¹⁷ Despite of the mild conditions of solid-supported cross-metathesis, its application to the chalcone synthesis has not yet been reported. In this work we have developed an efficient solid-supported methodology useful for generating libraries of chalcones and an alkane metathesis¹⁸ based on a tandem, one-pot, ruthenium-catalyzed cross-metathesis and reduction,¹⁹ to obtain biologically interesting β -phenylpropiofenone derivatives.²⁰

We initially analyzed the ruthenium catalyzed cross-metathesis between polymer supported 4-vinylbenzoic acid (**4**{1}) and nonimmobilized α,β -unsaturated ketones **5**{1–6} to obtain the corresponding chalcones (**6**{1,1–6}) (Scheme 1).

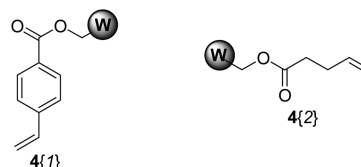
Scheme 1. Strategy for the Solid-Phase Synthesis of Chalcones



To study the cross-metathesis reaction, we chose olefin **5**{1} as a model substrate and two different ruthenium-carbene precatalysts [Grubbs' second generation (**7**) and Hoveyda-Grubbs' (**8**)] (Scheme 2 and Figure 2). While resin **4**{1} was obtained by coupling 4-vinyl benzoic acid to Wang resin by a standard coupling procedure, nonimmobilized olefin **5**{1} was synthesized, starting from anisole (**9**{1}), by a sequence Friedel-Crafts acylation/dehydrohalogenation (Scheme 2). Thus, anisole (**9**{1}) was treated with 3-bromopropionyl chloride (**10**) in the presence of aluminum chloride to obtain the 3-bromopropanone derivative **11**{1}. This Friedel-Crafts acylation was followed by the dehydrohalogenation using triethylamine to obtain α,β -unsaturated ketone **5**{1}.

Regarding the cross-metathesis coupling, every time precatalyst **7** was employed under a variety of reaction conditions, no desired product was detected, leaving the unreacted starting olefin **4**{1}. However, when precatalyst **8** was used, formation of the expected chalcone (**6**{1,1}) was successful. This promising result was clearly observed through gel-phase ¹³C NMR experiments [55.6 (OMe), 124.1 (CH-

Polymer supported olefins **4**



Non-immobilized olefins **5**

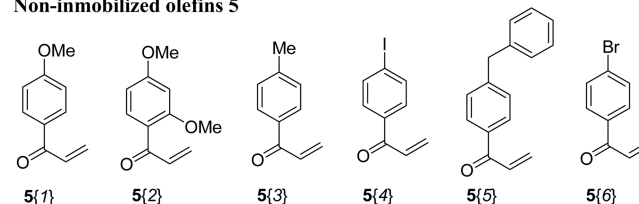


Figure 2. Structures and numbering of building blocks.

vinyl), 142.3 (CH-vinyl), 174.3 (CO, ester), 203.8 ppm (CO, ketone)]. After a short optimization process, the best conditions for this reaction were established: resin **4**{1} was treated with 5 mol % of precatalyst **8** and 5 equiv of olefin **5**{1} in toluene at 75 °C for 1 h.

A library of chalcones was then developed employing the synthetic pathway described above. The products were cleaved from the resin by treatment with 10% trifluoroacetic acid in CH₂Cl₂ during 1 h at room temperature and the carboxylic acid moiety was esterified with diazomethane. To our surprise, the analysis of the reaction crudes by ¹H NMR showed a mixture of compounds consisting in the desired chalcones and unknown byproducts. Besides, yields of the isolated chalcones **14**{1,1–3} were lower than we expected (entries 1–3, Table 1). Interestingly, in the case of compound **5**{4} (R¹ = I, R² = H, entry 4), after cleavage, methylation and purification by column chromatography, we isolated a product that, after analysis by ¹H NMR, ¹³C NMR, 2D NMR experiments and mass spectrometry, was unequivocally assigned as the 2-pyrazoline **12**{1,4} (Figure 3). This type of compounds could be generated by an 1,3-dipolar cycloaddition of diazomethane to the α,β -unsaturated double bond.²¹

To avoid the formation of byproducts derived from the use of diazomethane, we decided to directly purify compounds **13**{1,1–6} which contains the free carboxylic acid moiety (Table 1, entries 5–9). The corresponding chalcones were

Scheme 2. Solid-Phase Synthesis of Chalcones Based on Olefin Cross-Metathesis

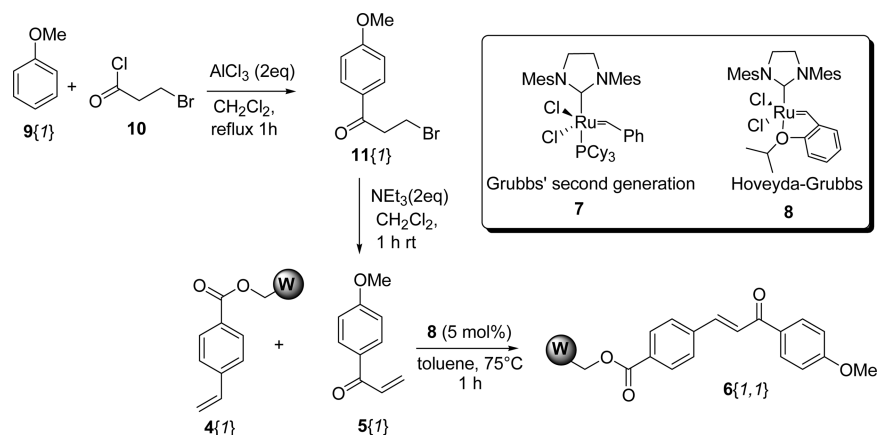
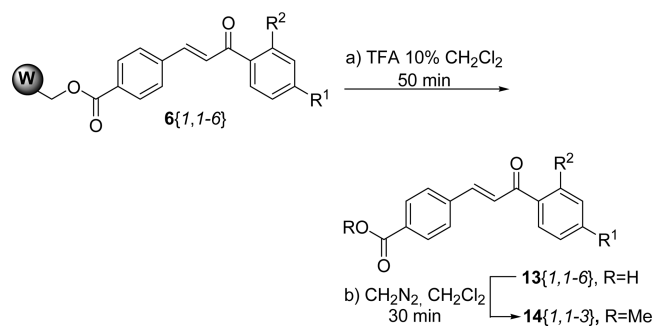


Table 1. Solid-Phase-Based Library of Chalcones



entry	R ¹	R ²	product	yield (%)
1	OMe	H	14{1,1}	36 ^a
2	OMe	OMe	14{1,2}	55 ^a
3	Me	H	14{1,3}	35 ^a
4	I	H	12{1,4}	36 ^a
5	OMe	H	13{1,1}	83 ^b
6	Me	H	13{1,3}	78 ^b
7	I	H	13{1,4}	65 ^b
8	CH ₂ Ph	H	13{1,5}	85 ^b
9	Br	H	13{1,6}	63 ^b

^aOverall isolated yield after flash column chromatography (based on loading of resin 4{1}). ^bOverall isolated yield after reverse-phase flash column chromatography (based on loading of resin 4{1}).

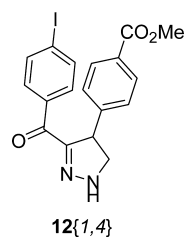


Figure 3. 2-Pyrazoline obtained by reaction of the corresponding chalcone and diazomethane.

obtained in very good overall yields, after isolation by reverse phase column chromatography.

Once the immobilized chalcones 6{1,1–6} were successfully achieved, we decided to hydrogenate these α,β -unsaturated alkenes to obtain biologically interesting β -phenylpropiofenone derivatives. The synthetic pathway chosen was a “hydrogen-free” reduction of α,β -unsaturated alkenes employing carbene-ruthenium precatalyst in a nonmetathetic role and Et₃SiH as reducing agent.¹⁹ Using previously reported conditions, which are based on Grubbs’ second generation catalysis (7) and microwave heating,¹⁹ the immobilized chalcone 6{1,1} was selectively reduced to the corresponding

immobilized saturated ketone 15{1,1} (Scheme 3). The appearance of methylene signals (30.3 and 39.5 ppm) instead of the vinyl ones (142.3 and 124.1 ppm) in the gel phase ¹³C NMR of resin 15{1,1} provided evidence of the convenience of this strategy. Final release from the solid support, methylation and isolation by column chromatography afforded 16{1,1} in 47% yield for the sequential cross-metathesis/olefin reduction process (Scheme 3). Additionally, we found that catalyst replacement by Hoveyda-Grubbs (8) gave compound 16{1,1} in similar yield.

To improve the efficiency of the whole sequence, we tried a one-pot cross-metathesis/reduction version.²² Since precatalyst 7 was inefficient for the cross-metathesis step, the one-pot strategy was performed using precatalyst 8. Thus, the solid-supported olefin 4{1}, precatalyst 8, and the nonimmobilized olefin 5{1}, suspended in anhydrous dichloromethane, were irradiated under microwave conditions during 10 min at 75 °C. After this time, the microwave vial was purged with nitrogen to remove the generated ethylene and the reaction was irradiated again for 20 min. Then, triethylsilane was added and the reaction mixture was irradiated during 30 min at 150 °C. Under this one-pot protocol, a small library of β -phenylpropiofenone 16{1,1–5} was afforded in good overall yields, after releasing from the resin, methylation and isolation by column chromatography (entries 1–4, Table 2). Unfortunately, when 1-(4-bromo-phenyl)-propenone (5{6}) was used as the solution-phase olefin, decomposition products were obtained after cleavage (entry 5). The efficacy of our formal alkane metathesis methodology was also demonstrated varying the starting immobilized olefin. With this purpose, 4-pentenoic acid linked to Wang resin (4{2}), preparing by standard DIC/DMAP coupling, was subjected to the optimal one-pot conditions with nonimmobilized olefins 5{1–5} to generate the saturated methyl esters 18{1,1–5} with very good overall yields (entries 6–9, Table 2).

In summary, we report an efficient solid-supported protocol toward the generation of libraries of biologically relevant chalcone scaffolds. This is the first cross-metathesis-based chalcone synthesis applying solid phase, which is especially useful for cross-coupling reaction because of the spatial separation of substrates achieved by immobilization on the resin, that avoids undesired homocoupling products. In addition, a formal alkane metathesis was developed by a tandem, one-pot, microwave-assisted, ruthenium-catalyzed cross-metathesis and reduction. This remarkable procedure was successfully applied to the synthesis of biologically interesting β -phenylpropiofenone and other acetophenone derivatives. We think that this study is an important contribution for a more general application of solid-phase strategies, particularly to the generation of C_{sp}³–C_{sp}³ bonds,

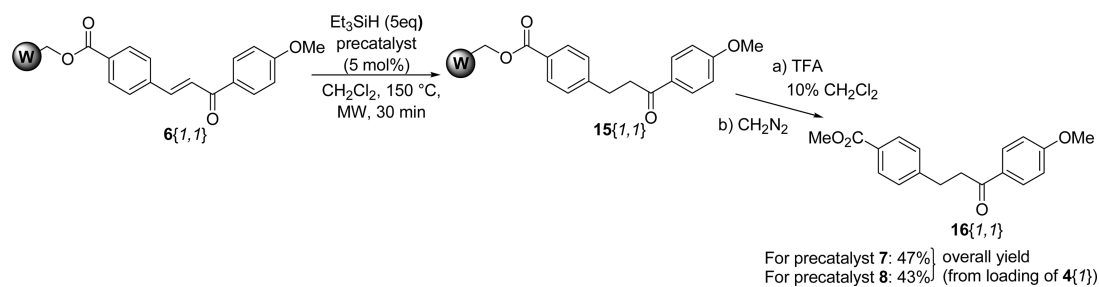
Scheme 3. Hydrogen-Free Reduction of α,β -Unsaturated Ketones by Ruthenium Precatalyst and Et₃SiH

Table 2. Formal Alkane Metathesis by Solid-Phase, One-Pot Cross-Metathesis/Reduction

entry	starting immobilized resin	R ¹	R ²	product	yield (%)
1	4{1}	OMe	H	16{1,1}	40 ^a
2	4{1}	Me	H	16{1,3}	34 ^a
3	4{1}	I	H	16{1,4}	32 ^a
4	4{1}	CH ₂ Ph	H	16{1,5}	40 ^a
5	4{1}	Br	H	16{1,6}	- ^b
6	4{2}	OMe	H	18{1,1}	50 ^c
7	4{2}	Me	H	18{1,3}	46 ^c
8	4{2}	I	H	18{1,4}	30 ^c
9	4{2}	CH ₂ Ph	H	18{1,5}	60 ^c

^aOverall isolated yield after flash column chromatography (four steps based on loading of resin 4{1}). ^bAfter cleavage decomposition products were obtained. ^cOverall isolated yield after flash column chromatography (five steps based on loading of Wang resin).

which are progressively more required for increasing F_{sp} value in the search for new drug candidates.

EXPERIMENTAL PROCEDURES

Representative procedure for the solid-phase synthesis of chalcones: Resin-bound vinyl benzoic acid 4{1} (100 mg, 0.11 mmol) was placed in a 25 mL round-bottom flask, purged with dry nitrogen, suspended in anhydrous toluene (3.0 mL) and olefin 5{5} (166.6 mg, 0.55 mmol) dissolved in anhydrous toluene (3.0 mL) was added via syringe. After addition of precatalyst 8 (3.4 mg, 5.5 μ mol, 5 mol %), the flask was fitted with a condenser with a cannula adapted so as to allow the elimination of the generated ethylene during the reaction. Being a reversible process, elimination of ethylene helps to displace the reaction toward the desired products.^{4b} The system was heated at 75 °C for 1 h under nitrogen atmosphere. Resin was filtered and washed with toluene (3 \times 5 mL), CH₂Cl₂ (3 \times 5 mL), MeOH (3 \times 5 mL), and CH₂Cl₂ (3 \times 5 mL) and dried under high vacuum. Resin 6{1,5} (98.5 mg, 77.8 μ mol, 0.79 mmol/g) was treated with 5 mL of 10% TFA in CH₂Cl₂ for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude product. The solvent was evaporated under reduced pressure and the crude material was purified by flash reversed column chromatography (H₂O–acetonitrile) to provide 13.4 mg of chalcone 13{1,5} (85% yield, calculated yield from linker 4{1}).

Representative procedure for one-pot cross-metathesis/reduction: Immobilized vinyl benzoic acid 4{1} (100 mg, 0.11 mmol) was placed in a 10 mL microwave vial, precatalyst 8 (3.4 mg, 5.5 μ mol, 5 mol %) and olefin 5{5} (166.6 mg, 0.55 mmol) dissolved in anhydrous CH₂Cl₂ (2 mL) were added under nitrogen atmosphere. The vial was placed in the microwave reactor with the appropriate cover. The reaction was irradiated during 10 min at 75 °C (maximum power = 300 W) in closed system with magnetic stirring. After this time the vial was removed from the microwave reactor and was purged with nitrogen in order to remove the generated ethylene. Then, the reaction was irradiated 20 min more under the same conditions. The vial was removed from the reactor, triethylsilane (88 μ L, 0.55 mmol) was added and the reaction

medium was irradiated during 30 min at 150 °C (maximum power = 300 W). Resin was filtered and washed with CH₂Cl₂ (3 \times 5 mL), AcOEt (3 \times 5 mL), MeOH (3 \times 5 mL), and CH₂Cl₂ (3 \times 5 mL) and dried under high vacuum. Resin 15{1,5} (112.6 mg, 83.3 μ mol, 0.74 mmol/g) was treated with 5 mL of 10% TFA in CH₂Cl₂ for 1 h. The mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude product. This crude material was dissolved in CH₂Cl₂ and treated with ethereal solution of diazomethane at 0 °C until yellowish coloration is achieved. The reaction was stirred for 30 min and diazomethane was quenched by addition of AcOH until discoloration was achieved. The solvent was evaporated under reduced pressure and the crude material was purified by flash column chromatography (hexane–AcOEt) to provide 6.3 mg of 16{1,5} (40% yield, calculated yield from linker 4{1}).

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data: ¹H NMR and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: mata@iquir-conicet.gov.ar. Fax: +54 341 4370477.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Support from CONICET, ANPCyT, and Universidad Nacional de Rosario from Argentina is gratefully acknowledged.

REFERENCES

- (1) Testero, S. A.; Mata, E. G. Prospect of Metal-Catalyzed C–C Forming Cross-Coupling Reactions in Modern Solid-Phase Organic Synthesis. *J. Comb. Chem.* **2008**, *10*, 487–497.
- (2) Young, D. D.; Deiters, A. *Solid-Phase Organic Synthesis: Concepts, Strategies, and Applications*; Toy, P. H., Lam, Y., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2012; pp 171–201.

(3) (a) Yan, B.; Sun, Q. Crucial Factors Regulating Site Interactions in Resin Supports Determined by Single Bead IR. *J. Org. Chem.* **1998**, *63*, 55–58. (b) Kraus, M. A.; Patchorn, A. Reactive Species Mutually Isolated on Insoluble Polymeric Carriers. II. The Alkylation of Esters. *Isr. J. Chem.* **1971**, *9*, 269–271. (c) Jayalekshmy, P.; Mazur, S. Pseudodilution, The Solid-Phase Immobilization of Benzynes. *J. Am. Chem. Soc.* **1976**, *98*, 6710–6711. (d) Ford, W. T. Site Isolation Organic Synthesis in Polystyrene Networks. *ACS Symp. Ser.* **1986**, *308*, 247–285. (e) Mazur, S.; Jayalekshmy, P. Chemistry of Polymer-Bound *o*-Benzynes. Frequency of Encounter between Substituents on Crosslinked Polystyrenes. *J. Am. Chem. Soc.* **1979**, *101*, 677–683.

(4) (a) Young, D. D.; Deiters, A. A General Approach to Chemo- and Regioselective Cyclotrimerization Reactions. *Angew. Chem., Int. Ed.* **2007**, *46*, 5187–5190. (b) Poeylout-Palena, A. A.; Mata, E. G. Unravelling the Olefin Cross Metathesis on Solid Support. Factors Affecting the Reaction Outcome. *Org. Biomol. Chem.* **2010**, *8*, 3947–3956. (c) La-Venia, A.; Testero, S. A.; Mischne, M.; Mata, E. G. Gold Catalysis on Immobilized Substrates: A Heteroannulation Approach to the Solid-Supported Synthesis of Indoles. *Org. Biomol. Chem.* **2012**, *10*, 2514–2517. (d) Traficante, C. I.; Delpiccolo, C. M. L.; Mata, E. G. *ACS Comb. Sci.* **2014**, *16*, 211–214.

(5) (a) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. Diversity-Oriented Synthesis As a Tool for the Discovery of Novel Biologically Active Small Molecules. *Nat. Commun.* **2010**, *1*, 80. (b) O'Connor, C. J.; Laraia, L.; Spring, D. R. Chemical Genetics. *Chem. Soc. Rev.* **2011**, *40*, 4332–4345. (c) Beckmann, H.; O'Connor, C. J.; Spring, D. R. Diversity-Oriented Synthesis: Producing Chemical Tools for Dissecting Biology. *Chem. Soc. Rev.* **2012**, *41*, 4444–4456.

(6) Nadin, A.; Hattotuwigama, C.; Churcher, I. Lead-Oriented Synthesis: A New Opportunity for Synthetic Chemistry. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114–1122. (b) MacLellan, P.; Nelson, A. A Conceptual Framework for Analysing and Planning Synthetic Approaches to Diverse Lead-like Scaffolds. *Chem. Commun.* **2013**, *49*, 2383–2393.

(7) For reviews, see: (a) Nandy, J. P.; Prakesch, M.; Khadem, S.; Reddy, P. T.; Sharma, U.; Arya, P. Advances in Solution- and Solid-Phase Synthesis toward the Generation of Natural Product-like Libraries. *Chem. Rev.* **2009**, *109*, 1999–2060. (b) Gil, C.; Bräse, S. Solid-Phase Synthesis of Biologically Active Benzoannulated Nitrogen Heterocycles: An Update. *J. Comb. Chem.* **2009**, *11*, 175–197.

(8) (a) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2007. *J. Comb. Chem.* **2008**, *10*, 753–802. (b) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2008. *J. Comb. Chem.* **2009**, *11*, 739–790. (c) Dolle, R. E.; Le Bourdonnec, B.; Worm, K. A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. Comprehensive Survey of Chemical Libraries for Drug Discovery and Chemical Biology: 2009. *J. Comb. Chem.* **2010**, *12*, 765–806.

(9) Tsukamoto, T. Tough Times for Medicinal Chemists: Are We to Blame? *ACS Med. Chem. Lett.* **2013**, *4*, 369–370.

(10) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752–6756.

(11) (a) Clemons, P. A.; Bodycombe, N. E.; Carrinski, H. A.; Wilson, J. A.; Shamji, A. F.; Wagner, B. K.; Koehler, A. N.; Schreiber, S. L. Small Molecules of Different Origins Have Distinct Distributions of Structural Complexity That Correlate with Protein-Binding Profiles. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 18787–18792. (b) Sauer, W. H. B.; Schwarz, M. K. Molecular Shape Diversity of Combinatorial Libraries: A Prerequisite for Broad Bioactivity. *J. Chem. Inf. Comp. Sci.* **2003**, *43*, 987–1003. (c) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. What Do Medicinal Chemists Actually Make? A 50-Year Retrospective. *J. Med. Chem.* **2011**, *54*, 6405–6416.

(12) For representative examples, see: (a) Joshi, D.; Parikh, K. S. Synthesis and Antimicrobial Evaluation of 1,3,4-Oxadiazole-Based Chalcone Derivatives. *Med. Chem. Res.* **2014**, *23*, 1855–1864.

(b) Mallavadhani, U. V.; Sahoo, L.; Kumar, K. P.; Murty, U. S. Synthesis and Antimicrobial Screening of Some Novel Chalcones and Flavanones Substituted with Higher Alkyl Chains. *Med. Chem. Res.* **2014**, *23*, 2900–2908. (c) Zangade, S. B.; Jadhav, J. D.; Vibhute, Y. B.; Dawane, B. S. Synthesis and Antimicrobial Activity of Some New Chalcones and Flavones Containing Substituted Naphthalene Moiety. *J. Chem. Pharm. Res.* **2010**, *2*, 310–314. (d) Liu, X. L.; Xu, X. J.; Go, M. L. Functionalized Chalcones with Basic Functionalities Have Antibacterial Activity against Drug Sensitive *Staphylococcus aureus*. *Eur. J. Med. Chem.* **2008**, *43*, 1681–1687.

(13) (a) Sivakumar, P. M.; Muthu-Kumar, T.; Doble, M. Antifungal Activity, Mechanism and QSAR Studies on Chalcones. *Chem. Biol. Drug Des.* **2009**, *74*, 68–79. (b) Lahtchev, K. L.; Batovska, D. I.; Parushev, S. P.; Ubiyovk, V. M.; Sibirny, A. A. Antifungal Activity of Chalcones: A Mechanistic Study Using Various Yeast Strains. *Eur. J. Med. Chem.* **2008**, *43*, 2220–2228.

(14) Asad, M.; Beevi, F.; Ganesan, S. P.; Oo, C. W.; Kumar, R. S.; Laxmipathi, V.; Osman, H.; Ali, M. A. Synthesis of Novel and Highly Functionalized 4-Hydroxycoumarin Chalcone and their Pyrazoline Derivatives as Anti-Tuberculosis Agents. *Letts. Drug Des. Discovery* **2014**, *11*, 222–230.

(15) (a) Rullah, K.; Aluwi, M. F. F. M.; Yamin, B. M.; Bahari, M. N. A.; Wei, L. S.; Ahmad, S.; Abas, F.; Ismail, N. H.; Jantan, I.; Wai, L. K. Inhibition of Prostaglandin E₂ Production by Synthetic Minor Prenylated Chalcones and Flavonoids: Synthesis, Biological Activity, Crystal Structure, and in Silico Evaluation. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3826–3834. (b) Lee, I.-S.; Lim, J.; Gal, J.; Kang, J. C.; Kim, H. J.; Kang, B. Y.; Choi, H. Anti-inflammatory Activity of Xanthohumol Involves Heme Oxygenase-1 Induction via NRF2-ARE Signaling in Microglial BV2 Cells. *J. Neurochem. Int.* **2011**, *58*, 153–160.

(16) For representative examples, see: (a) Zhang, E.; Wang, R.; Guo, S.; Liu, B. An Update on Antitumor Activity of Naturally Occurring Chalcones. *J. Evidence-Based Complementary Altern. Med.* **2013**, No. 815621. (b) Wang, G.; Peng, F.; Cao, D.; Yang, Z.; Han, X.; Liu, J.; Wu, W.; He, L.; Ma, L.; Chen, J.; Sang, Y.; Xiang, M.; Peng, A.; Wei, Y.; Chen, L. Design, Synthesis and Biological Evaluation of Millepachine Derivatives As a New Class of Tubulin Polymerization Inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 6844–6854. (c) Kolundija, B.; Markovi, V.; Stanojkovi, T.; Joksovi, L.; Mati, I.; Todorovi, N.; Nikoli, M.; Joksović, M. D. Novel Anthraquinone Based Chalcone Analogues Containing an Imine Fragment: Synthesis, Cytotoxicity and Anti-angiogenic Activity. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 65–71. (d) Abonia, R.; Insuasty, D.; Castillo, J.; Insuasty, B.; Quiroga, J.; Nogueras, M. Synthesis of Novel Quinoline-2-one Based Chalcones of Potential Anti-tumor Activity. *Eur. J. Med. Chem.* **2012**, *57*, 29–40. (e) Kumar, D.; Kumar, M.; Akamatsu, K.; Kusaka, E.; Harada, H.; Ito, T. Synthesis and Biological Evaluation of Indolyl Chalcones As Antitumor Agents. *Bioorg. Med. Chem.* **2010**, *20*, 3916–3919. (f) Insuasty, B.; Tigreros, A.; Orozco, F.; Quiroga, J.; Abonia, R.; Nogueras, M.; Sánchez, A.; Cobo, J. Synthesis of Novel Pyrazolic Analogues of Chalcones and Their 3-Aryl-4-(3-aryl-4,5-dihydro-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazole Derivatives As Potential Antitumor Agents. *Bioorg. Med. Chem.* **2010**, *18*, 4965–4974.

(17) For solid-phase synthesis of chalcones, see: (a) Marzinzik, A. L.; Felder, E. R. Key Intermediates in Combinatorial Chemistry: Access to Various Heterocycles from α,β -Unsaturated Ketones on the Solid Phase. *J. Org. Chem.* **1998**, *63*, 723–727. (b) Katritzky, A. R.; Serdyuk, L.; Chassaing, C.; Toader, D.; Wang, X.; Forood, B.; Flatt, B.; Sun, C.; Vo, K. Syntheses of 2-Alkylamino- and 2-Dialkylamino-4,6-diarylpyridines and 2,4,6-Trisubstituted Pyrimidines Using Solid-Phase-Bound Chalcones. *J. Comb. Chem.* **2000**, *2*, 182–185. (c) Katritzky, A. R.; Chassaing, C.; Barrow, S. J.; Zhang, Z.; Vvedensky, V.; Forood, B. Solid-Phase Synthesis of 4,6-Disubstituted and 3,4,6-Trisubstituted Pyrid-2-ones. *J. Comb. Chem.* **2002**, *4*, 249–250. (d) Wagman, A. S.; Wang, L.; Nuss, J. M. Simple and Efficient Synthesis of 3,4-Dihydro-2-pyridones via Novel Solid-Supported Aza-Annulation. *J. Org. Chem.* **2000**, *65*, 9103–9113. (e) Sensfuss, U. Solid-Phase Aldol Condensations Mediated by Zinc Acetate and 2,2'-Bipyridine under

Weakly Basic Conditions. *Tetrahedron Lett.* **2003**, *44*, 2371–2374.

(f) Neves, M. P.; Cravo, S.; Lima, R. T.; Vasconcelos, M. H.; Nascimento, M. S. J.; Silva, A. M. S.; Pinto, M.; Cidade, H.; Correa, A. G. Solid-Phase Synthesis of 2'-Hydroxychalcones. Effects on Cell Growth Inhibition, Cell Cycle and Apoptosis of Human Tumor Cell Lines. *Bioorg. Med. Chem.* **2012**, *20*, 25–33.

(18) Haibach, M. C.; Kundu, S.; Brookhart, M.; Goldman, A. S. Alkane Metathesis by Tandem Alkane-Dehydrogenation–Olefin-Metathesis Catalysis and Related Chemistry. *Acc. Chem. Res.* **2012**, *45*, 947–958.

(19) Poeylout-Palena, A. A.; Testero, S. A.; Mata, E. G. The Non-metathetic Role of Grubbs' Carbene Complexes: From Hydrogen-Free Reduction of α,β -Unsaturated Alkenes to Solid-Supported Sequential Cross-Metathesis/Reduction. *Chem. Commun.* **2011**, *47*, 1565–1567.

(20) Ohno, O.; Ye, M.; Koyama, T.; Yazawa, K.; Mura, E.; Matsumoto, H.; Ichino, T.; Yamada, K.; Nakamura, K.; Ohno, T.; Yamaguchi, K.; Ishida, J.; Fukamizu, A.; Uemura, D. Inhibitory Effects of Benzyl Benzoate and Its Derivatives on Angiotensin II-Induced Hypertension. *Bioorg. Med. Chem.* **2008**, *16*, 7843–7852.

(21) Parai, M. K.; Panda, G. A Convenient Synthesis of Chiral Amino Acid Derived 3,4-Dihydro-2H-benzo[*b*][1,4]thiazines and Antibiotic Levofloxacin. *Tetrahedron Lett.* **2004**, *45*, 4703–4705.

(22) For a very recent example of conventional heating, one-pot isomerization-cross metathesis-reduction, see: Jida, M.; Betti, C.; Schiller, P. W.; Tourwé, D.; Ballet, S. One-Pot Isomerization-Cross Metathesis-Reduction (ICMR) Synthesis of Lipophilic Tetrapeptides. *ACS Comb. Sci.* **2014**, *16*, 342–351.