avec ou sans extraction d'eau (réacteurs 1 et 3) sont à peu près identiques;

- la présence de méthanol en excès dans le milieu réactionnel est un facteur très limitant;
- l'utilisation de faible concentration de méthanol (réacteur 2) permet d'éviter la désactivation de la résine. Cela se traduit par une vitesse de réaction nettement supérieure à celles constatées en opérant dans les réacteurs (1) et (3).

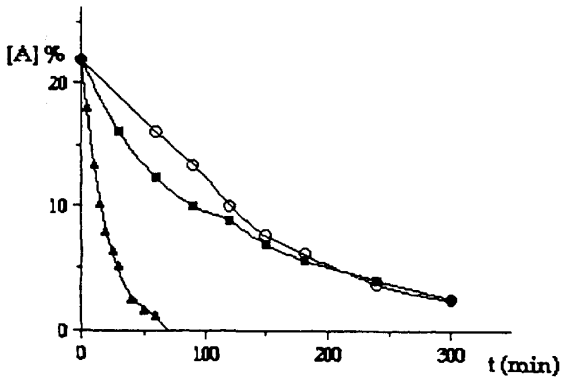

Fig 2. Neutralisation de l'huile de grignon d'olive par le méthanol. Comparaison des techniques expérimentales. o : réacteur (1); ▲ : réacteur (2); □ : réacteur (3).

Conclusion

Cette étude montre que l'estérification des acides gras libres d'une huile végétale catalysée par une résine échangeuse d'ions est fortement limitée par la présence d'un excès d'alcool dans le milieu réactionnel. La solvatation des sites actifs par l'alcool conduit à la désactivation du catalyseur et entraîne l'inhibition de la réaction.

Par ailleurs, nous avons montré que cette réaction peut se faire avec une faible concentration de méthanol ou d'éthanol dans un réacteur ouvert fonctionnant à une température largement supérieure à la température d'ébullition de l'alcool. Dans ces conditions, la solvatation des sites actifs du catalyseur est très peu probable. La réaction devient alors rapide.

La neutralisation des huiles végétales dans ce réacteur est facile à mettre en œuvre et présente de nombreux avantages, parmi lesquels nous pouvons citer à titre d'exemple :

- la réduction considérable des temps de réaction;
- l'extraction instantanée de l'eau du milieu réactionnel qui entraîne le déplacement de l'équilibre chimique de l'estérification et conduit à l'amélioration du rendement de la réaction;
- l'utilisation de l'alcool à très faible concentration, qui permet d'obtenir directement les produits de la réaction par simple filtration de la résine. L'étape de séparation de l'alcool de la phase lipidique ne s'avère plus nécessaire.

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A palladium-catalyzed route to chiral 1,2,3-trisubstituted cyclopropanes

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Summary — An easy and efficient method for the synthesis of 1,2,3-trisubstituted vinylic cyclopropanes is described. The key steps are alkylation of chiral allylic alcohols, cyclization of functionalized allylic substates using a palladium(0) catalyst and decarboalkoxylation.

alkylation / cyclopropanation / decarboalkoxylation / palladium(0) catalyst / chiral vinylic cyclopropane

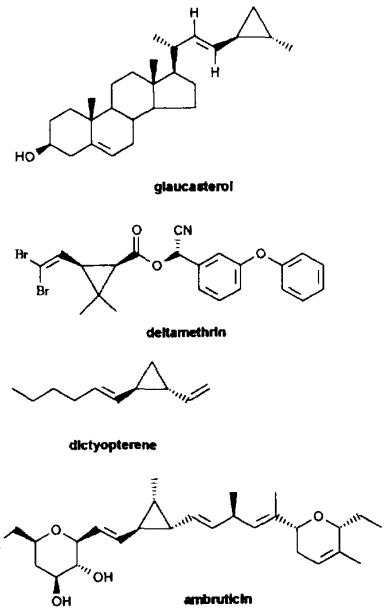
Résumé — Synthèse de cyclopropanes chiraux 1,2,3-trisubstitués catalysée au palladium. *Une méthode simple et efficace de synthèse de cyclopropanes vinyliques trisubstitués est décrite. Les étapes clés sont l'alkylation d'alcools allyliques chiraux, la cyclopropanation de composés allyliques fonctionnalisés à l'aide de catalyseurs au palladium(0) et la déalcoxycarbonylation de cyclopropanes optiquement actifs.*

alkylation / cyclopropanation / déalcoxycarbonylation / catalyseur au palladium(0) / cyclopropane vinylique chiral

Introduction

The design and development of efficient methods for the stereoselective and asymmetric syntheses of substituted cyclopropanes have been the subject of a myriad [1] of investigations because of the presence of such subunits in a number of natural products and their use as key intermediates in multistep organic transformations. Vinylcyclopropanes are essential constituents of many naturally occurring vinylic cyclopropanes as carenes, sesquicarenes, sirenine, dictyopterenes, pyrethroids [1]. Most of the research in this field has been devoted to the control of the relative and absolute stereochemistry around the cyclopropane ring of several compounds such as glaucasterol [2], dictyopterene [3], deltamethrin [4] and ambruticin [5].

We have been interested in vinylcyclopropanes synthesis for a long time [6] and we have recently developed an efficient and practical synthesis of *cis* and *trans* vinylic cyclopropanes via an intramolecular $S_{N'}$ palladium(0)-catalyzed reaction [7a]. As seminal contributions from various groups have described methods for the asymmetric synthesis of disubstituted cyclopropanes [8a], there are few methods for the asymmetric synthesis of enantiomerically pure tri- and tetrasubstituted cyclopropanes [8b]. We describe herein a full account of our chiral cyclopropanation methodology, which affords absolute stereocontrol of three stereogenic centers leading to enantiomerically pure 1,2,3-trisubstituted cyclopropanes.



Our strategy, described in figure 1, starts from a chiral allylic alcohol **2**. The well-established sequential alkylation, cyclopropanation catalyzed by palladium(0) leads to a cyclopropane ring **5**. The *cis* or *trans* relationship between the vinylic and the methyl group of

* Correspondence and reprints

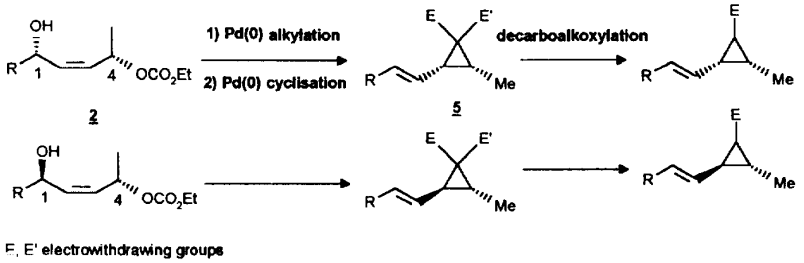


Fig 1

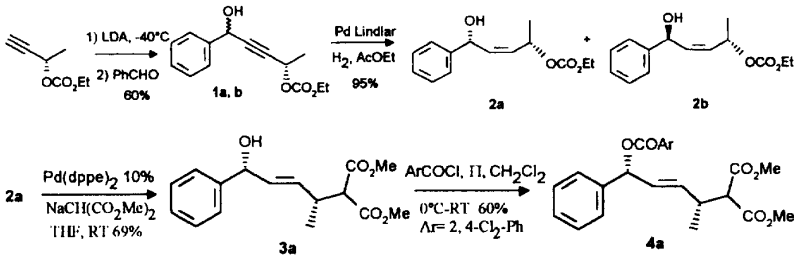


Fig 2

the cyclopropane **5** is induced by the choice of the chirality of the alcohol **2**. The decarboalkoxylation leads to 1,2,3-trisubstituted cyclopropanes.

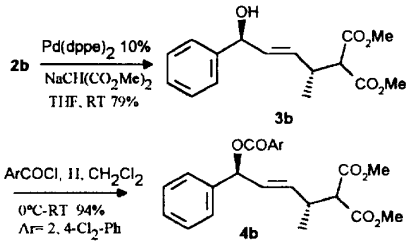
Results

Synthesis of the requisite enantiopure allylic alcohols **2** *and alkylation catalyzed with Pd(0)*

The alcohols **1a,b** were prepared by reaction of the (*S*)-ethyl (1-methylprop-2-ynyl)carbonate [9] with benzaldehyde. We were pleased to find that after the hydrogenation of the 1:1 mixture **1a,b** using Lindlar catalyst, the two *Z*-allylic alcohols **2a,b** could be separated by medium pressure liquid chromatography. Each *Z*-allylic alcohol **2** could undergo alkylation catalyzed by palladium(0) as shown in figure 2 for **2a**. The alkylation was easily conducted at room temperature and led to a single stereomer with a complete regio- and stereoselectivity. The alkylations of **2a** occurred on the carbon C_4 to give the chiral allylic compounds **3a** with exclusive *E* double bond stereochemistry and 69–80% yield. The high stereochemical control in the carbon-carbon bond formation may be attributed to the π-allyl palladium intermediate stability [7a]. The compounds **3a** were then converted into the corresponding benzoate **4a** with 2,4-dichlorobenzoyl chloride.

The alkylation of **2b** led to **3b** which was benzoylated to give **4b** with 74% yield in two steps.

The mechanism of the alkylation is described in figure 3 [7b,c]. The palladium attacks the double bond of the 1,4-allylic substrate opposite to the leaving group, with formation of the chiral *anti-syn* palladium intermediate. As this π-allylic intermediate is not symmetrically substituted, diastereoselection will be dictated by which face of the allylic fragment the transition metal



presents to the nucleophile. An π-σ-π-equilibrium between palladium intermediates leads to the most stable *syn-syn* π-allyl compound. Therefore the metal has switched between enantiofaces of the allylic fragment. On the timescale of a typical alkylation reaction, the *syn-anti* substituents in a palladium π-allyl complex can exchange positions faster than alkylation. The nucleophile then attacks from the face of the favored *syn-syn* π-allyl opposite to the palladium.

We also have conducted the sequential reactions of alkylation and protection on the two diastereomers **2c** and **2d** starting from the benzaldehyde and the (*R*)-but-3-yn-2-ol [9]. We have isolated the two enantiomers **3c** and **3d** of **3a** and **3b**; the activated alcohol **4c** and **4d** were then prepared in good yields. The chemical characteristics of all the diastereomers (α_D, ^{13}C-NMR, ^{1}H-NMR, IR, MS) were in complete accordance as described in the *Experimental section.*

Cyclopropanation

The cyclopropanation was conducted with Pd(dppe)$_2$ as catalyst and DBU as base in THF at room temperature. The palladium-promoted $S_{N'}$ cyclization of the functionalized allylic benzoates **4a** afforded the cyclopropane **5a** to which is attached a vinyl, a methyl and *gem*-dimethoxy esters with 90% yield.

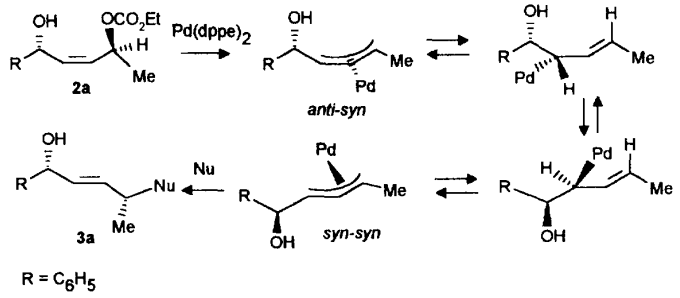
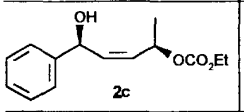
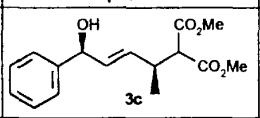
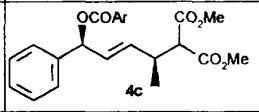
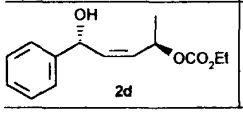
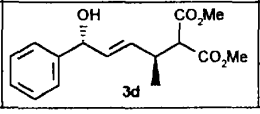
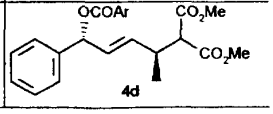


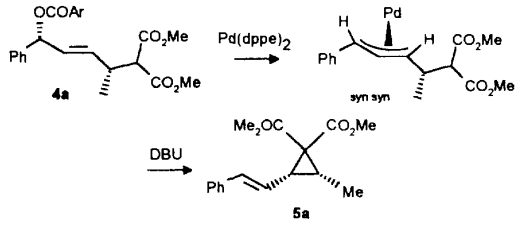
Fig 3

Compounds	Alkylated Compounds	Benzoyl Compounds
 2c	 3c	 4c
 2d	 3d	 4d

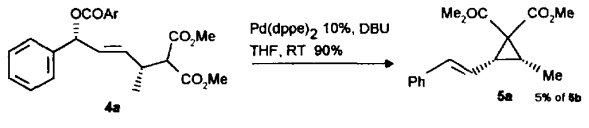
Ar = 2, 4-Cl_2-Ph

The transfer of the C-O chirality to the new C-C bond in the vinylic cyclopropanes proceeded smoothly. This strategy involves the following steps: the palladium attacks the double bond of the allylic substrate opposite to the leaving benzoate group, with formation of the chiral palladium intermediate; and the nucleophile attacks from the face of the π-allyl opposite to the palladium [10].

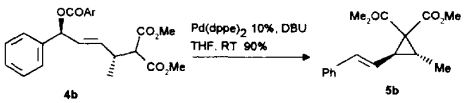
The process allows a net *syn* $S_{N'}$ replacement of the benzoate by the C-C bond in the cyclopropanes **5** in good yields and with high stereoselectivity.



The cyclopropane **5a** was obtained with 90% yield. We have used 250 MHz NMR to detect 5% of the *trans*-cyclopropane **5b**: a likely explanation for the loss of stereospecificity observed would be that the palladium(0) phosphine complex displaces the allyl-bound Pd(II) with inversion of configuration and then the cyclization would induce the formation of **5b** [6g,h, 7b,c].



The *trans* cyclopropane **5b** was obtained optically pure with no trace of the *cis* stereochemistry by 250 MHz NMR and with 90% yield.



The cyclopropane **5c** was isolated with high yields and 5% of the cyclopropane **5d**, whereas the cyclopropane **5d** was obtained with high stereoselectivity from **4d**.

Alkylation, cyclization with the tert*-butyl ethyl malonate*

We have thus established an efficient methodology to generate *cis*- and *trans*-vinyl cyclopropanes. We have also explored the cyclopropanation of *tert*-butyl ethyl malonyl intermediates. The choice of *tert*-butyl ethyl malonate is justified to study the stereocontrol on the third center during the cyclopropanation. The alkylation of **2b** using the *tert*-butyl ethyl malonate, followed by the protection of the alcohol, afforded the 1,4-functionalized compounds **4e,f**.

In the same way, **2a** was alkylated with 80% yield and the resulting mixture transformed into benzoate **4g,h**.

The mixture of **4e,f** underwent the cyclopropanation reaction. Unfortunately, the trisubstituted cyclopropanes **5e,f** were obtained as a 1:1 mixture with 74% yield. The unsaturated vinylic chain still has the *E* stereochemistry and the methyl and side chain groups have a *trans* relationship. Unfortunately, **5e,f** were inseparable by chromatography.