Pure & Appl. Chem., Vol. 62, No. 4, pp. 653–660 1990.
Printed in Great Britain.

New applications of organopalladium compounds in organic synthesis

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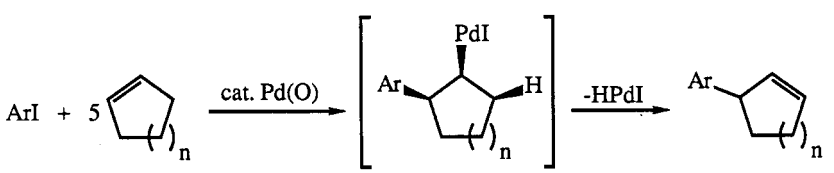
Abstract - The inter- and intramolecular palladium-catalyzed arylation and vinylation of cyclic alkenes provides a useful new route to 3-arylcycloalkenes and cyclic 1,4-dienes. Applications of this chemistry to the synthesis of inhibitors of blood platelet activating factor and prostaglandins are described. Taking advantage of the ability of palladium to migrate along carbon chains, one can easily prepare long chain aromatic aldehydes, ketones and other carbonyl-containing compounds. Palladium-promoted cyclization also affords novel new routes to unsaturated lactones, bicyclic acetals, benzofurans, indoles, quinolines and isoquinolines. Finally, palladium-catalyzed hetero- and carboannulation provides still another convenient route to hetero- and carbocycles.

INTRODUCTION

Organopalladium chemistry has become one of the most active areas of organometallic chemistry directed towards organic synthesis (refs. 1, 2). Our own recent work in this area has focused on (1) inter- and intramolecular arylation and vinylation of cyclic alkenes, (2) palladium migration chemistry and (3) cyclization and annulation chemistry. These areas will be reviewed in that order.

PALLADIUM-CATALYZED ALKYLATION OF CYCLIC ALKENES

A number of workers have reported the palladium-promoted arylation of cyclic alkenes using arylmercurials, aryl halides, aryl sulfinate salts, aryl diazonium salts or aryl amines (ref. 3). In general these reactions either require stoichiometry amounts of palladium, proceed in low yields or provide mixtures of double bond isomers. We have recently developed convenient procedures for such arylation using aryl halides and only catalytic amounts of palladium which overcome all of these previous difficulties (eq. 1).



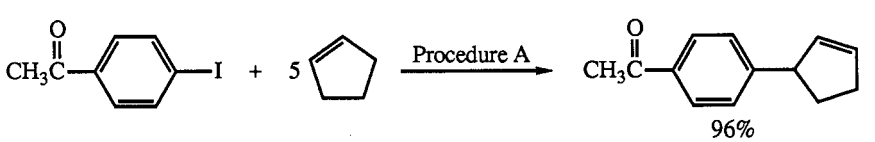
(1)

PROCEDURE A: 2.5% $Pd(OAc)_2$, *n*-Bu_4NCl, 3 KOAc

B: 3% $Pd(OAc)_2$, 9% PPh_3, 2 Ag_2CO_3

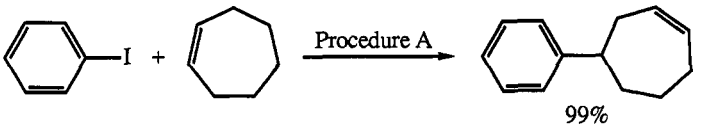
C: 2.5% $Pd(OAc)_2$, *n*-Bu_4NCl, 3 KOAc, 2.5% PPh_3

Procedure A works nicely using a variety of aryl halides and cyclic alkenes (eq. 2), but isomerization



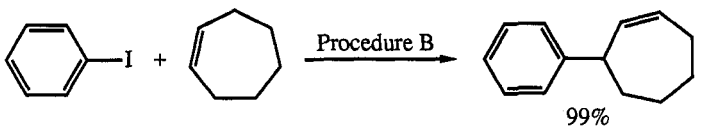
(2)

is a major problem when cycloheptene (eq. 3) or cyclic ethers are employed. Fortunately, these



(3)

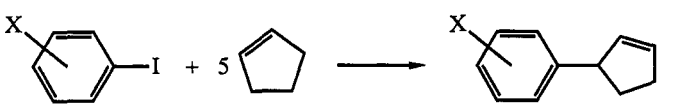
difficulties can be overcome by using a procedure, Procedure B, first reported by Overman (ref. 4) for similar intramolecular arylation processes (eq. 4, ref. 5). While this procedure was found to work well



(4)

for cyclic alkenes prone to isomerization, neither of these procedures works well for a number of functionally-substituted aryl halides. Fortunately, the addition of catalytic amounts of PPh_3 to Procedure A (Procedure C) gave excellent results for such aromatic halides (Table 1).

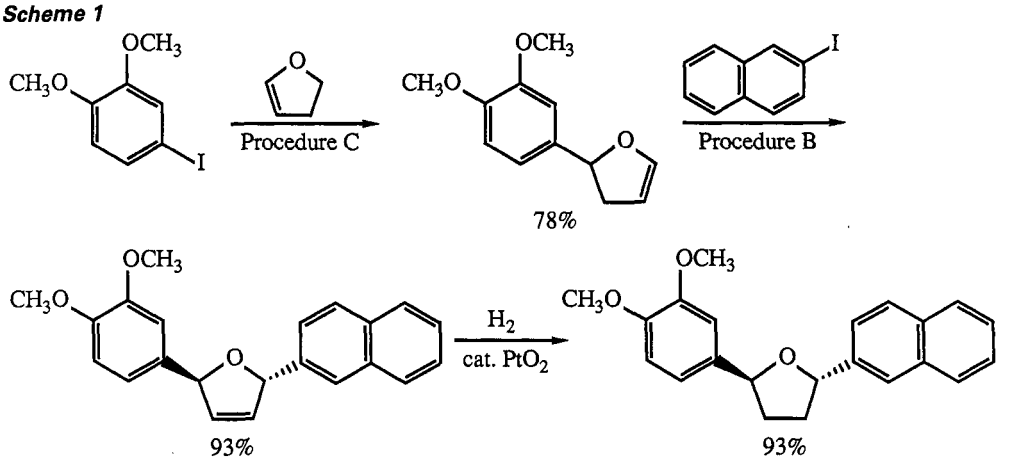
TABLE 1. Comparison of Procedures for the Synthesis of Functionally-Substituted 3-Arylcyclopentenes



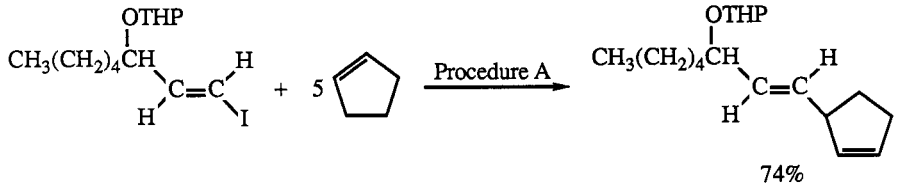
X	% Yield A	B	C
o-OH	42	0	66
o-NH_2	6	0	52
o-NHAc	0	0	76
o-CH_2OH	0	0	99
o-CHO	0	0	87
o-NO_2	0	70	90
p-NO_2	0	52	85

When employing Procedure C on cyclic vinylic ethers, such as 2,3-dihydrofuran, complete isomerization of the double bond around the ring was observed. This has provided a novel new route to inhibitors of blood platelet activating factor (ref. 6, Scheme I).

Scheme 1



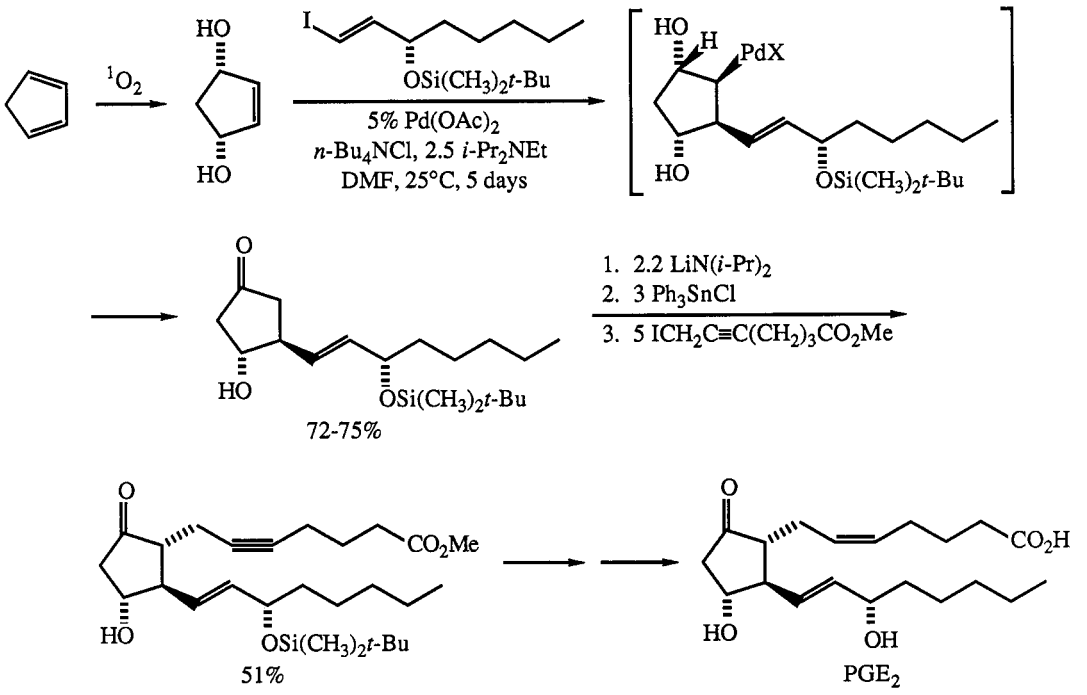
An analogous palladium-catalyzed intermolecular vinylation process has also recently been developed (eq. 5, ref. 7).



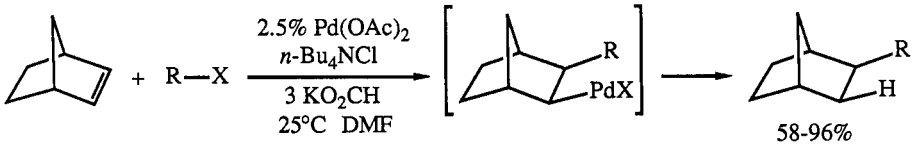
(5)

This chemistry has since been employed in an efficient synthesis of prostaglandin E2 (Scheme II, ref. 8).

Scheme 2



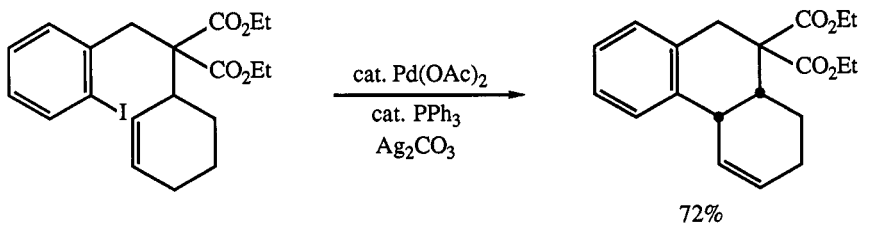
This chemistry also affords a convenient method for the arylation or vinylation of bicyclic alkenes when KO2CH is added as both a base and a reducing agent (eq. 6, ref. 9).



R = aryl, vinylic

(6)

Intramolecular variations of this chemistry have now been reported by several groups (refs. 4, 10 and 11) including ourselves (eqs. 7 and 8, ref. 12).



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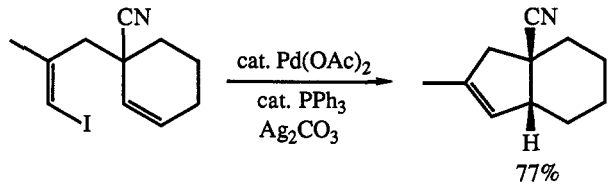

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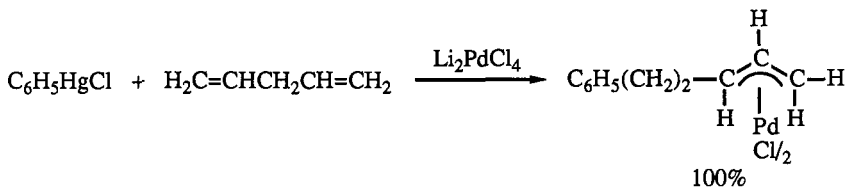
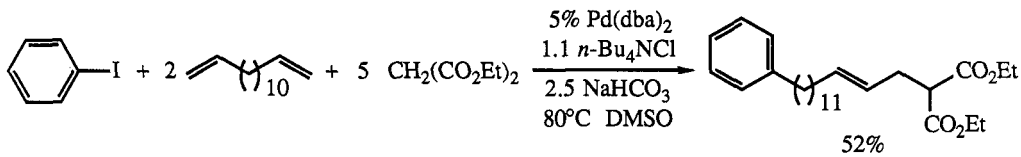
PALLADIUM MIGRATION CHEMISTRY

The ability of palladium to migrate along carbon chains by a process involving palladium hydride elimination and subsequent readdition with the opposite regiochemistry has been observed by several groups. We, for example, reported the convenient preparation of π-allylpalladium compounds by arylpalladium addition to non-conjugated dienes (eq. 9, ref. 13). The synthetic utility



(9)

of this process has recently been put to use in the construction of aryl-substituted long chain carbonyl compounds (eq. 10, ref. 14).



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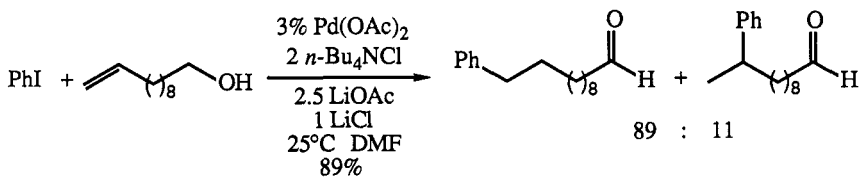
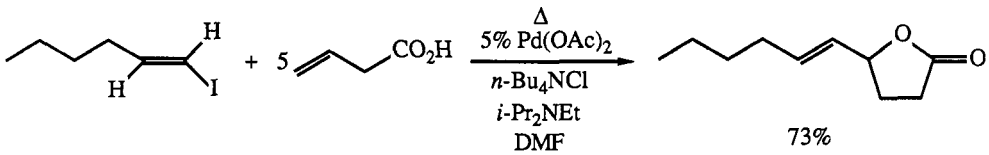
In a similar fashion, the arylation of long chain olefinic alcohols provides a novel approach to aryl aldehydes or ketones (eq. 11, ref. 15). This reaction no doubt proceeds by arylpalladation of the



(11)

alkene, palladium migration, and finally palladium hydride elimination to an enol which tautomerizes to the observed carbonyl product.

A related useful process employing palladium migration chemistry involves the coupling of vinylic halides or triflates with unsaturated carboxylic acids (eq. 12, ref. 16).



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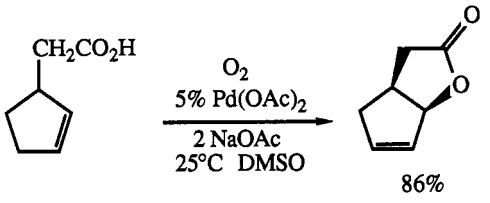
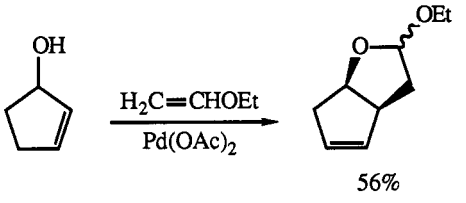
CYCLIZATION AND ANNULATION PROCESSES

Unsaturated lactones have also recently been prepared by the palladium(II)-catalyzed dehydrogenative lactonization of unsaturated carboxylic acids (eq. 13, ref. 17).



(13)

Bicyclic acetals are also readily available by palladium-promoted coupling of cyclic allylic alcohols, ethyl vinyl ether and $Pd(OAc)_2$ (eq. 14, ref. 18) using Utimoto's general procedure (ref. 19).



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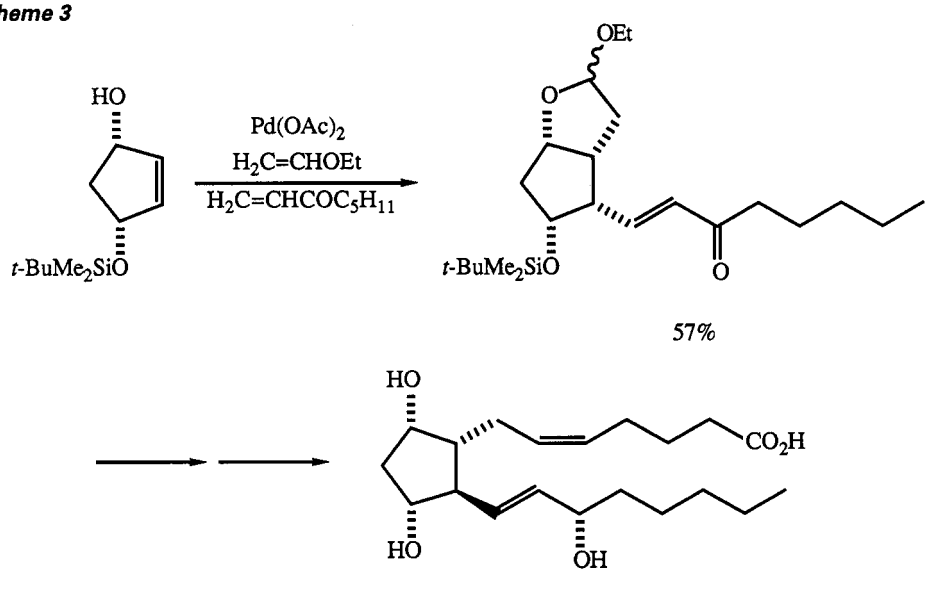
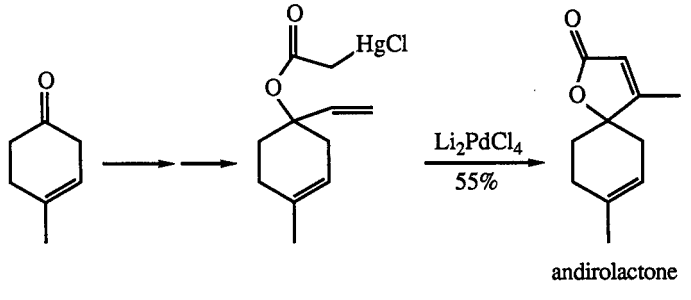
This chemistry has recently afforded a novel approach to prostaglandins (Scheme III, ref. 20). Since

Scheme 3



the key intermediate bicyclic acetal has previously been epimerized by E. J. Corey (ref. 21) and carried on to $PGF_{2\alpha}$, this constitutes a highly efficient formal synthesis of this prostaglandin.

Butenolides are also now readily available by the palladium-promoted cyclization of chloromercurio-acetate esters of acyclic allylic alcohols (eq. 15, ref. 22).



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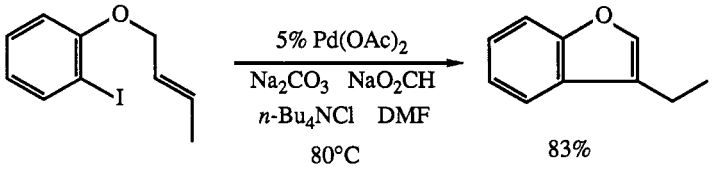
Similar palladium-catalyzed cyclization processes have recently been developed for the synthesis of benzofurans (eq. 16, ref. 23), indoles (eq. 17, ref. 24), quinolines and isoquinolines.



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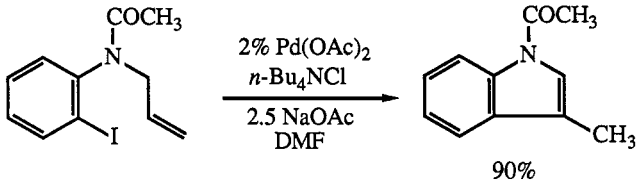
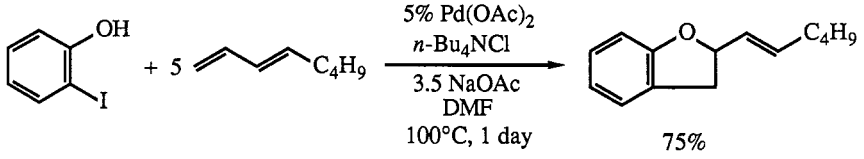


(17)

One of the most exciting recent developments in our laboratories has been the development of palladium-catalyzed processes for the heteroannulation of 1,3-dienes, 1,4-dienes, 1,2-dienes and alkynes (eqs. 18-21, ref. 25).



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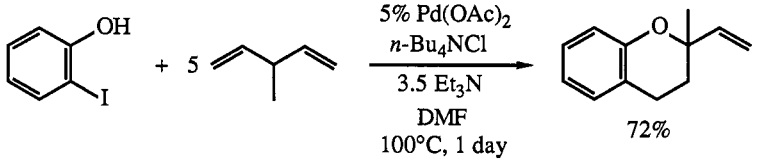

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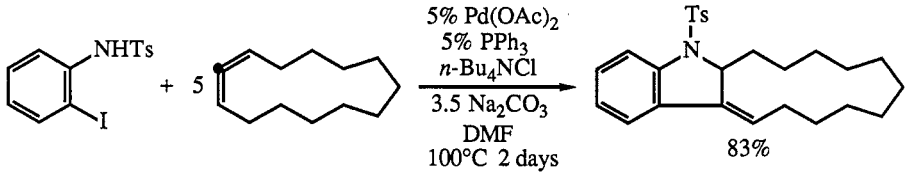

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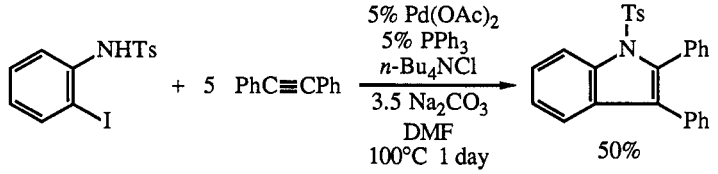

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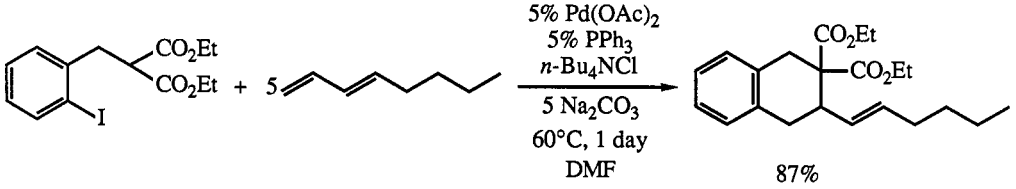
Analogous carboannulation processes can also be effected under very mild conditions in high yields (eqs. 22-25, ref. 26). Unlike analogous intermolecular π-allylpalladium displacement processes,



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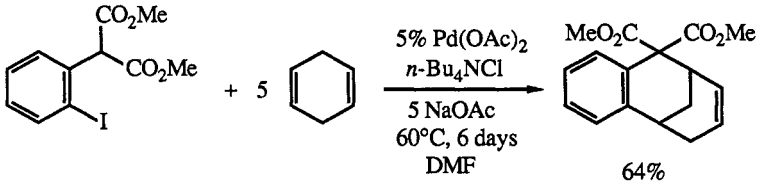

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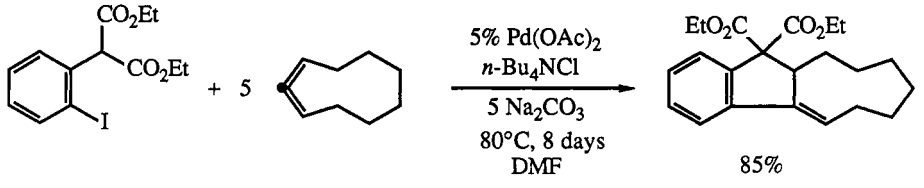

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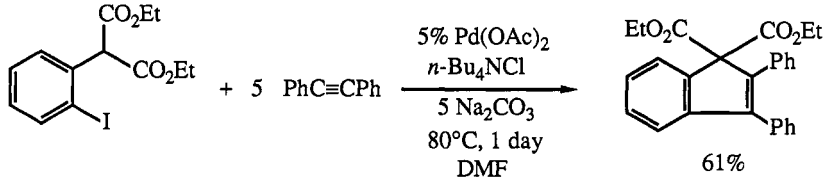
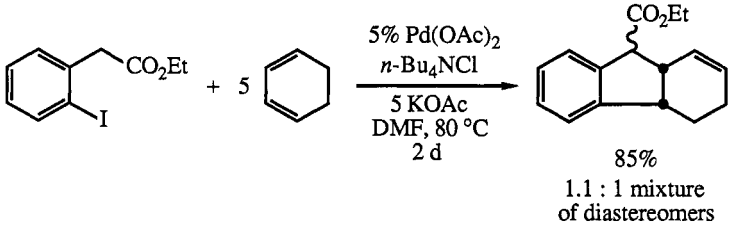


(25)

these intramolecular reactions can be effected using simple esters, ketones and nitro groups (eqs. 26-28). Vinylic halides can also be employed in these processes (eq. 29). These annulation processes appear extremely useful for the synthesis of a wide variety of hetero- and carbocycles.



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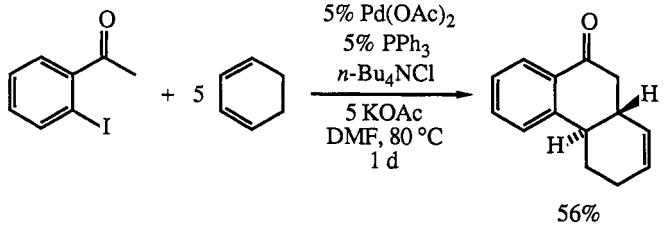

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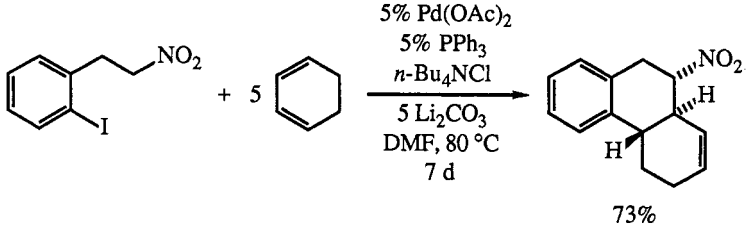

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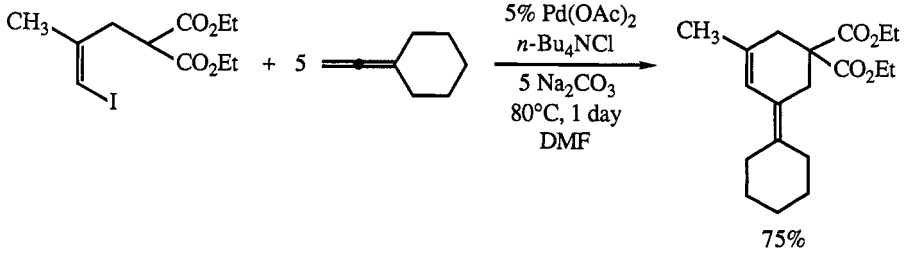

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CONCLUSION

A number of exciting new palladium-promoted carbon-carbon and carbon-heteroatom bond forming reactions have been recently developed. These synthetic transformations are unique. They proceed under mild reaction conditions in excellent yields. They require only catalytic amounts of palladium. They accommodate considerable organic functionality. They are sufficiently versatile to generate a wide variety of organic structures, and in many cases they involve the simultaneous formation of more than one new bond at a time. These reactions appear particularly promising for the synthesis of complex natural products.

Acknowledgements

We wish to gratefully acknowledge the Donors of the Petroleum Research Fund, administered by the American Chemical Society, the American Heart Association-Iowa Affiliate, and the National Institutes of Health for their generous support of our research. Our thanks also go out to Johnson Matthey, Inc. and Kawaken Fine Chemicals Co. Ltd. for kindly providing the palladium salts used in this work.

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