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A simple method to prepare single isomer tetrasubstituted olefins by successive Suzuki–Miyaura cross-couplings of *E*-β-chloro-α-iodo-α,β-unsaturated esters

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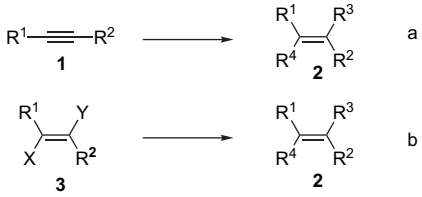
ABSTRACT

A convenient method of synthesizing tetrasubstituted olefins as single isomers is described. *E*-β-Chloro-α-iodo-α,β-unsaturated esters are first converted into the corresponding *E*-β-chloro-α,β-unsaturated esters using Suzuki–Miyaura coupling reactions with arylboronic acids and alkenylboronic acids. These transformations gave complete selectivity, and proceeded with substitution at the more activated α-iodide position. These compounds, isolated as single isomers, were then transformed into tetrasubstituted olefins by Suzuki–Miyaura couplings with arylboronic acids, alkenylboronic acids, and alkyl boranes to afford the corresponding tetrasubstituted olefins as single isomers. During this coupling process, it was discovered that the use of small ligands, such as PMe_3 or PEt_3, was critical for efficient coupling. The stereochemistry and regiochemistry of the products were unequivocally established using NMR methods.

1. Introduction

The efficient regio- and stereodefined synthesis of tetrasubstituted olefins bearing four different carbon-linked appendages presents a significant challenge.[1] The congested nature of the double bond often makes it difficult for reagents to approach each other, reducing the utility of many 'traditional' olefin-producing reactions. The majority of the methods that have been developed to produce tetrasubstituted olefins rely either on the carbometallation of alkynes or on the use of olefin templates in cross-coupling reactions. Alkyne carbometallation is perhaps the most widely used method,[1,2] and because of the convergent nature of the strategy, in principle it provides maximum structural variation (Scheme 1a). Tetrasubstituted double bonds can also be prepared by manipulating a pre-existing olefin template (Scheme 1b).[1,3] Generating the template is often the most difficult aspect of this approach, requiring the installation of directing elements for chemo-, regio-, and stereocontrol. Selectivity issues may arise during the subsequent cross-coupling stages that can lead to the production of isomeric mixtures that may be extremely difficult to resolve.

Many natural products[4] and pharmaceuticals[3b,5,6] contain tetrasubstituted olefins as important structural elements. Tetrasubstituted olefins can also be used as intermediates in asymmetric transformations that generate quaternary centers such as osmylations,[7] epoxidations,[8] and conjugate additions.[9] Compounds containing tetrasubstituted alkenes have been employed as dipeptide mimetics[10] as well as polymerization substrates and catalysts.[11] Material science makes use of these functionalities because of their physical,[12] structural, and electronic properties;[13] and these moieties have often been used to form molecular switches[14] or optical storage devices.[15] All of these applications require preparative chemical transformations that are reliable, simple to perform, and that deliver the products as single isomers.



Scheme 1. General strategies for tetrasubstituted olefin formation.

We have recently developed a mild and versatile method of synthesizing acyclic, single isomer olefins bearing four different carbon-linked substituents.[16] These alkenes were obtained using a differentially halogenated template that was submitted to sequential Sonogashira coupling reactions to produce trans ene–diynes. Herein, we describe the optimization of sequential Suzuki coupling reactions to these templates using arylboronic acids and alkylboranes, a challenging task given the steric demands of the substrates and reagents. An extensive package of tetrasubstituted olefins formed by a simple, regioselective and stereoselective, three-step method is disclosed as well.

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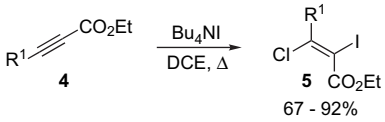
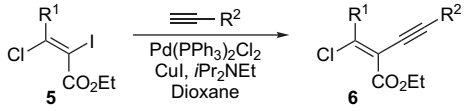
2. Results and discussion

The efficient synthesis of *E*-β-chloro-α-iodo-α,β-unsaturated esters by the exposure of 2-alkynyl esters to Bu_4NI in refluxing dichloroethane represents a versatile entry into tetrasubstituted olefin production.[17] This method gives β-chloro-α-iodo olefin templates such as **5** with complete control of regio- and stereochemistry. This process is directed by the presence of an electron-withdrawing group on the alkyne and provides the starting point for subsequent organometallic coupling reactions that convert the template into a single isomer, all carbon-linked alkene (Scheme 2).



Scheme 2. Generation of single isomer *E*-β-chloro-α-iodo-α,β-unsaturated esters.

The introduction of substituents onto the *E*-β-chloro-α-iodo templates can be done selectively and smoothly. Sonogashira reactions were first explored to obtain intermediate trisubstituted olefins, a task that required some optimization in order to obtain good yields and, importantly, single isomers.[16] Starting with templates **5**, submission to typical Sonogashira conditions produced the desired products **6** that were isolated as single isomers in good yield (Scheme 3).



Scheme 3. Sonagashira coupling of *E*-β-chloro-α-iodo-α,β-unsaturated esters to produce trisubstituted olefin templates.

These results were significant in that they demonstrated that selectivity could be achieved in the cross-coupling of dihalogenated templates such as **5**. Of particular interest was the facile and preferential displacement of the α-iodo substituent. Related templates bearing identical halogens at both the α- and β-position invariably react at the more activated β-position first,[18] a trend reversed in the present series due to the increased reactivity of the iodide relative to the chloride.

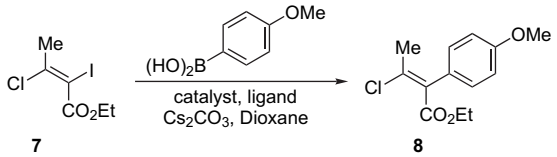
Encouraged by our success with the Sonogashira coupling reaction, efforts were then directed to the development of a Suzuki coupling process[19] in order to introduce a larger variety of nucleophiles at the α-position of substrate **7** (Table 1). The testing of a variety of palladium catalyst precursors suggested that selectivity was possible in this process, however the efficiency of the reaction was very sensitive to the palladium source. The use of $PdCl_2(PPh_3)_2$ (entry 3) gave a moderate improvement in yield compared to the $Pd_2(dba)_3$ that was used originally (entry 1), while the use of $Pd(dppf)Cl_2$ alone resulted in a lower product recovery (entry 2). Using $Pd(OAc)_2$ as a palladium source (entry 4) afforded the highest yield when using P^tBu_3 as the ligand.

Using the best conditions described above as a starting point, an optimization of the reaction solvent was then performed (Table 2). Interestingly, the use of polar solvents such as acetonitrile (entry 1), DMSO (entry 2) or DMF (entry 3) did not lead to any of the desired product. Performing the reaction in other common solvents such as THF, benzene or $CHCl_3$ gave modest amounts of product, but the use of these solvents did not produce any advantages over the dioxane originally used (entries 4–9). A slight but significant increase in the yield of the monosubstituted product **8** was realized when reactions were performed in EtOAc or in toluene (entries 10–12), with toluene giving the best conversion to products.

During these optimization studies, significant amounts of the tetrasubstituted olefin were produced. Because this product was the result of an over-reaction at the β-position, we investigated the possibility of improving the selectivity by lowering the reaction temperature. As shown in Table 3, lowering the temperature of the reaction to 0 °C did not lead to any improvement in reaction selectivity (entry 2). Raising the temperature slightly, however, resulted in a significant increase in the amount of tetrasubstituted product **10** that was formed (entry 3). As there was no advantage in lowering the reaction temperature compared to performing the reactions at room temperature, the more practical conditions were employed for the next set of experiments.

The ligand was found to have a profound impact on reaction efficiency (Table 4). Initial experiments were carried out using $Pd(OAc)_2$ and $P^tBu_3\cdot HBF_4$. These conditions delivered a modest yield of the desired product **9**, together with a small amount of tetrasubstituted adduct **10** (entry 1). Reducing the size of the ligand resulted in the production of significant amounts of the double-coupled material (entries 2–4). Unfortunately, the use of other hindered ligands such as PCy_3 did not improve selectivity, nor did the use of PPh_3 or bidentate ligands such as DPPF (entries 5–7). Use of the biphenyl ligand *S*-PHOS produced a remarkably selective reaction (entry 8), a result that was unequaled by a related ligand

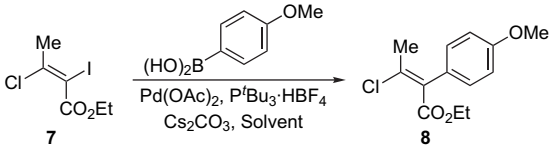
Table 1
Effect of the palladium source in Suzuki coupling reactions at the α-position of **7**



Entry[a]	Catalyst	Ligand	Yield[b] (%)
1	$Pd_2(dba)_3$	$P^tBu_3\cdot HBF_4$	17
2	$Pd(dppf)Cl_2$	—	10
3	$PdCl_2(PPh_3)_2$	$P^tBu_3\cdot HBF_4$	35
4	$Pd(OAc)_2$	$P^tBu_3\cdot HBF_4$	45

[a] Conditions: 0.1 equiv of catalyst, 0.2 equiv of ligand, 4.0 equiv of boronic acid, 4.0 equiv of Cs_2CO_3, and dioxane, 23 °C.
[b] Tetrasubstituted (15–25%) olefin was also obtained in each of these reactions.

Table 2
Effect of the solvent in the Suzuki coupling reactions of **7**



Entry[a]	Solvent	Yield (%)
1	CH_3CN	NR
2	DMSO	NR
3	DMF	NR
4	CH_2Cl_2	Trace
5	THF	26
6	Benzene	17
7	$CHCl_3$	34
8	Trifluorotoluene	38
9	^{t}BuOMe	35
10	Dioxane	45
11	EtOAc	50
12	Toluene	60

[a] Conditions: 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of $P^tBu_3\cdot HBF_4$, 4.0 equiv of boronic acid, 4.0 equiv of Cs_2CO_3, and 23 °C.