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Journal of Organometallic Chemistry 253 (2002) 279–287

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

Mini-review

Application of cross-coupling reactions in Merck

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Received 27 July 2001; accepted 22 September 2001

Abstract

Process design and development of drug candidates using cross-coupling reactions as key steps are discussed. In the anti-MRS carbapenem project, all drug candidates were prepared effectively in a few steps from the commercially available diazo intermediate by either Suzuki–Miyaura cross-coupling or Stille–Migita cross-coupling, demonstrating the versatility, effectiveness, functional group tolerability, and mild reaction conditions of cross-coupling methods.

Keywords: Cross-coupling; Suzuki–Miyaura; Stille–Migita; Stannatrane; Carbapenem; Pharmaceutical

1. Introduction

Progress on cross-coupling reactions has strongly impacted the pharmaceutical industry in many ways. For drug discovery, advances in cross-coupling technology have provided new avenues for drug design over conventional chemical methods to optimize drug activity, pharmacokinetics, and safety. Cross-coupling reactions are quite effective for dissecting a target molecule into smaller modules. Especially, in light of the blossoming of combinatorial approaches, cross-coupling reactions provide great diversity of chemical structure for lead identification and optimization of drug candidates. On the other hand, for process development and manufacture of drug substances, cross-coupling reactions provide opportunities to develop environmentally friendly and economically sound manufacturing processes in a shorter time period. This is of great importance in allowing us to provide effective medicines to society at affordable prices with the earliest timing, while maintaining a safe living environment. In other words, progress on cross-coupling reactions saves patients from life threatening diseases and dramatically improves their quality of life.

Some of the processes for Merck drugs (Cozaar® [1]; Maxalt® [2]; Singulair® [3]) contain cross-coupling reactions as key steps. Key dissection positions for these drugs are indicated in Fig. 1. Since there is not enough space to discuss these processes, only references are provided. Cross-coupling reactions for drug candidates of the anti-methicillin resistant *Staphylococcus* (MRS) carbapenem class are discussed in detail herein.

2. Carbapenem project

First observed in the 1960s [4], MRS has become a worldwide problem, especially in areas where potent antibiotics have been heavily used. In such MRS infections, vancomycin has become the primary treatment despite its adverse side effects. The search for alternative therapies is driven by the expected emergence of vancomycin-resistance to *S. aureus* from a resistant *Enterococcus*, which has been demonstrated in the laboratory. Recently, infections by vancomycin-intermediate-resistant *Staphylococcus aureus* have been reported.

Since the mid-1980s, Merck has been interested in developing anti-MRS drugs. This effort has resulted in the discovery of four potent anti-MRS carbapenem drug candidates. Their structures are depicted in Fig. 2. Since several advanced carbapenem intermediates are commercially available in large quantities and it is quite burdensome to manipulate compounds containing a β-lactam ring, cross-coupling reactions with advanced carbapenem intermediates are methods of choice in

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PII: S0022-328X(02)01263-9

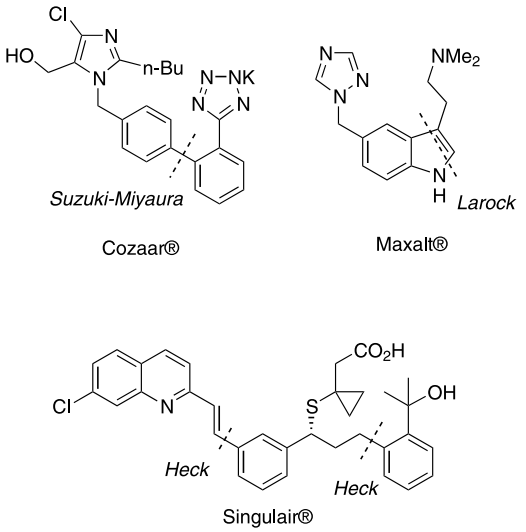


Fig. 1. Merck's drugs using cross-coupling as key reactions.

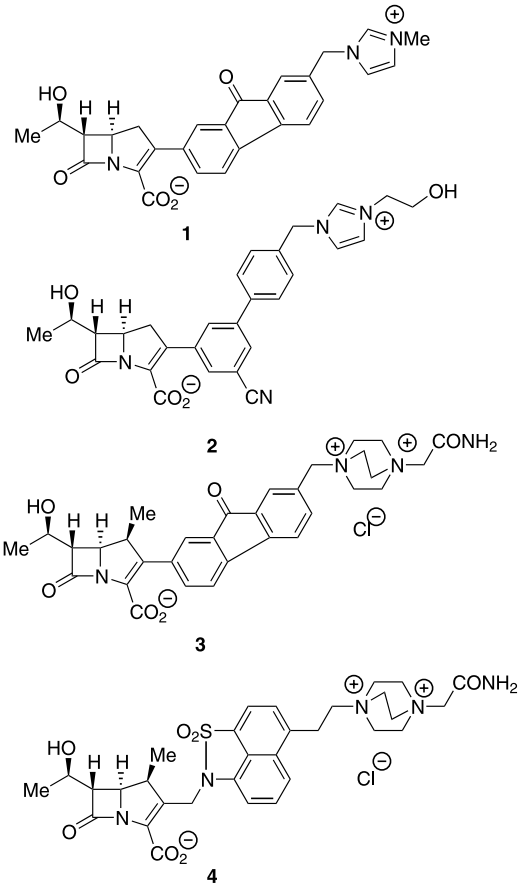


Fig. 2. Anti-MRS carbapenem candidates.

this field. The first three compounds **1**–**3** have a common chemical structural feature, namely 2-aryl carbapenem [5]. For these candidates, boronic acid mediated Suzuki–Miyaura cross-coupling reactions between sp^2 and sp^2 carbons were the key reactions in these processes. The last candidate **4** was designed based on the releasing hapten theory [6]. Stille–Migita cross-coupling reaction was the key reaction to form a sp^2–sp^3 carbon–carbon bond [7].

2.1. Aryl carbapenems

2.1.1. Introduction

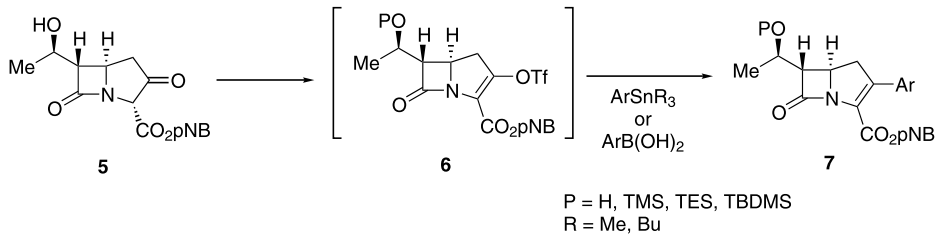
The first candidate **1** contained a fluorenone ring, which was attached at the carbapenem C-2 position by a carbon-carbon bond. The fluorenone ring was further substituted with an *N*-methylimidazolium moiety at a distal position. The initial crystalline form of **1** had reasonable water solubility (100 mg ml^{-1}), but later a new crystal form (trihydrate) was discovered. Its water solubility was very poor (<0.7 mg ml^{-1}) due to the zwitter ionic character of the molecule. The second candidate **2** contained a biphenyl group at C-2 position with a *N*-hydroxyethylimidazolium moiety at the terminus. This candidate also suffered from low water solubility, in spite of the additional hydroxyl group. In order to increase water solubility, another quaternary ammonium moiety was introduced in the next candidate **3**, along with introduction of a β-methyl group at C-1 position which increased chemical stability.

2.1.2. Chemistry

At the beginning of this project, preparation of this class of compounds relied on the Mukaiyama aryl ketone formation followed by Woodward cyclization [5a]. This method was quite efficient but also required many chemical steps. In 1990 the Merck Medicinal Chemistry group reported preparation of this class of compounds by an aryl trimethyltin mediated Stille–Migita cross-coupling method [5b]. This coupling was highly efficient with excellent yield under neutral conditions at room temperature. Initially, candidate **1** was prepared by this method.

In the beginning of this project, it was believed the Suzuki–Miyaura cross-coupling reaction would not be applicable in this case since carbapenems are generally thought to be unstable under the reaction conditions (basic aqueous at elevated temperature). Consequently, a less toxic aryl tributyltin derivative was prepared but the cross-coupling reaction with the aryl tributyltin provided the product in lower yield than that with the corresponding trimethyltin. More alkyl group transfer was observed in reaction. At the same time, it was found that the carbapenem 2-triflate derivative **6** was stable under basic conditions and was unstable under acidic conditions. These physical characteristics are ideal for the Suzuki–Miyaura cross-coupling. The coupling conditions were optimized and generalized [5c] (Scheme 1). This method has successfully been applied to candidates **1** and **2** with a minor modification.

Nickel catalyzed cross-coupling of the enol tosylate with boronic acids has been reported [5e]. Cross-



Scheme 1.

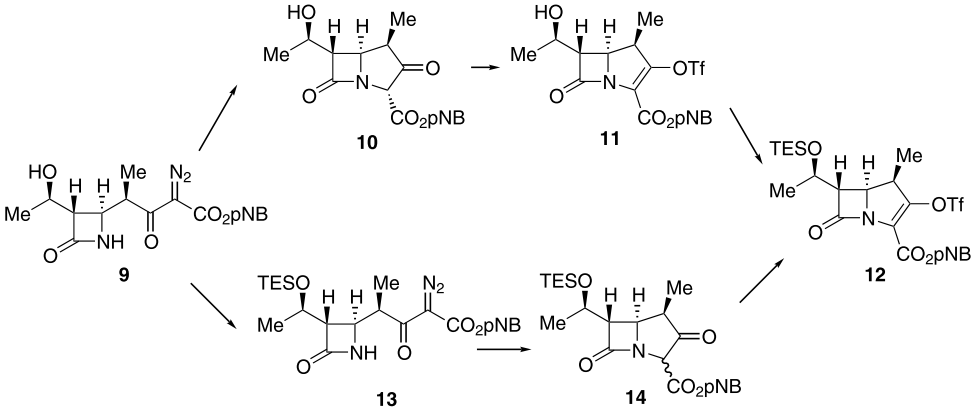
coupling reactions with the commercially available enol phosphate **8** [8] is highly desirable, however, no cross-couplings were observed under any conditions.

Here, chemistry for the drug candidate **3** will be reviewed in more detail [5d].

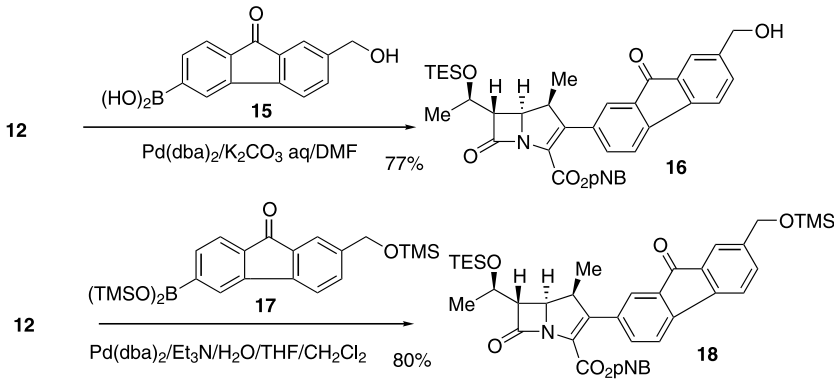
2.1.2.1. Carbapenem enol triflate (β-methyl). Since **3** has a β-methyl group at the C-1 position, the preparation of the corresponding triflate **12** was somewhat different (Scheme 2). At the beginning, the commercially available crystalline diazo compound **9** was converted to the bicyclic compound **10** in the presence of rhodium octanoate and zinc bromide, which was then directly converted to the corresponding enol triflate **11** below −70 °C. Triflate **11** was extremely unstable even at −78 °C. After protection of the secondary alcohol by addition of TESOTf below −78 °C, the TES enol triflate **12**, which had reasonable stability, was obtained and used in situ for the next cross-coupling reactions.

Stability of enol triflates increase when bulkier silicon protective groups are introduced at the secondary alcohol. The TES group was selected based on the stability of the enol triflate and on mildness of the subsequent deprotection conditions. While efficient for multigram synthesis, this sequence did not perform well on multi-kilogram scale. The exothermic character of both the triflation and silylation steps required very slow additions to maintain the temperature below −70 °C, and during this time significant decomposition of the unprotected enol triflate **11** occurred. To bypass the most unstable intermediate **11**, we opted to silylate the secondary alcohol prior to cyclization. TES diazo compound **13** was obtained as a stable crystalline compound. Rhodium catalyzed cyclization provided the stable bicyclic compound **14**. Unlike unprotected cases, **14** exists as a mixture of epimers at the C-3 position (α:β = 97:3) by NMR and HPLC. Formation of the enol triflate was also somewhat different. The best yield (98%) and stability of the enol triflate **12** was obtained when a combination of 0.35 equivalents of TEA and one equivalent of diisopropylamine was used, and triflation was done at −40 °C.

2.1.2.2. Cross-coupling. Initial cross-coupling efforts employed the simple fluoroenone boronic acid **15** (Scheme 3). The previously developed conditions were successful, with the only modification being substitution of DMF for THF because of the solubility of **15**. A major problem with this method during scale-up was the ability to obtain the prodict **16** as a crystalline solid without chromatography. Subsequently, it was found that its TMS derivative **18** crystallized well from methanol. Therefore, boronic acid **15** was silylated with 3 equiv of *N*,*O*-bis(trimethylsilyl)acetamide in THF prior to cross-coupling. The resulting homogeneous solution of fully silylated material **17** was effective for cross-coupling with enol triflate **12** in CH_2Cl_2/THF. However, the usual cross-coupling conditions employing aqueous inorganic base caused substantial desilyation of the hydroxymethyl position and limited the isolated yield. Milder conditions employing two equivalents of TEA as base and only two equivalents of water



Scheme 2.



Scheme 3.

limited the desilylation and allowed isolation of **18** without chromatography in 80% yield. The cross-coupled product **18** was successfully converted to the candidate **3** using conventional chemical steps.

In order to reduce chemical transformations in the presence of the carbapenem skeleton, the more ambitious goal would be cross-coupling between enol triflate **12** and the doubly quaternized boronic acid **19**. This approach initially proved fruitless, primarily due to the poor solubility properties of **19** and its borate salts. Because of the highly charged character of **19**, a solvent mixture of DMF and water was essential for the reaction. The counterion of the base was also critical for success. Lithium carbonate was found to be the best base, with potassium and cesium carbonates being much worse. This trend is the opposite of the usual cation influence observed by us and others, and it correlates with borate solubility.

A further critical factor turned out to be the quantity of bromide ion; bromide typically constituted a portion of the counterion of the boronic acid **19**. The highest coupling rate was observed with ca. 0.2 molar equivalents of bromide. Either larger or smaller quantities slowed the reaction, and no coupling occurred in the absence of halide.

With the proper choice of solvents and base, high-yielding cross-coupling occurred at 30–35 °C. Because the TES-containing product **20** was difficult to isolate, it was directly converted to the desilylated product **21** as a bis-triflate salt in 60% isolated yield from the TES protected diazo compound **13**. Desilylated product **21** was readily converted to the candidate **3** in one step (Scheme 4).

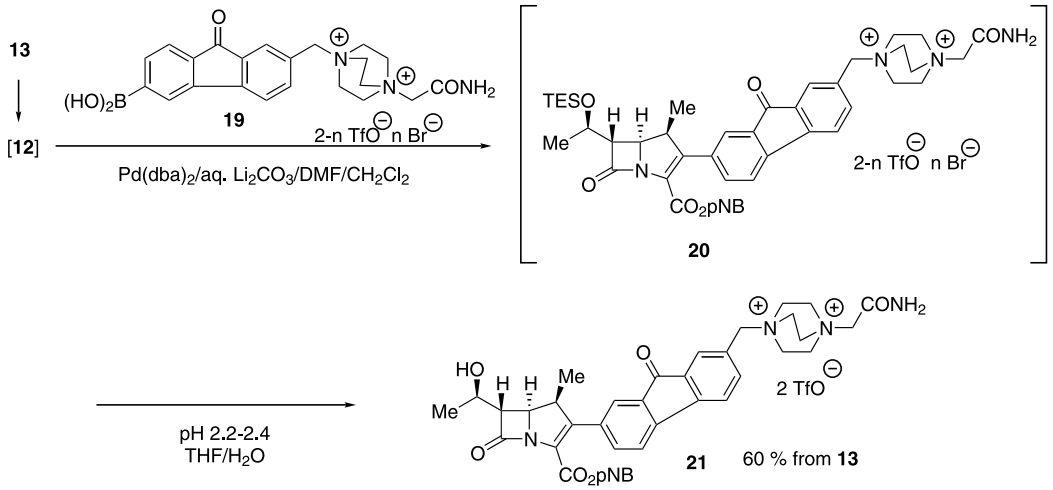
2.2. Releasable side chain carbapenem

Drug candidate **4** was designed employing a releasable side chain concept [6,7a,7b]. The key intermediate of the initial route for these class of compounds was the bis(allyl)-protected carbapenem **22**, which was prepared from acetoxyazetidinone in 12 steps and was an unstable oil. The instability was due to formation of a five-membered lactone, releasing allyl alcohol. Unlike the cephalosporin cases, the resulting tricyclic lactone was unstable and spontaneously decomposed with release of its high strain energy. Furthermore, final deprotection was problematic. Under McCombie's conditions [9], allyl ester and allyloxycarbonyl (alloc) were cleanly deprotected, but about 4% of the side chain also rearranged from the terminal position to the C-3 position because of the low pK_a of the side chain (Scheme 5). The rearranged product was difficult to remove from the desired product [10]. Therefore, we decided to change the protecting group to *p*-nitrobenzyl (pNB).

2.2.1. 2-Hydroxymethyl carbapenem pNB ester

Initially, the chemical stability of a 2-hydroxymethyl pNB ester was a serious concern because of the better leaving ability of pNBOH over allyl alcohol. On the other hand, pNB esters are generally highly crystalline. The desired pNB ester was first prepared from 4-(4-bromo-3-oxo-2-butyl)azetidinone [7d] via Woodward cyclization and was found to be a crystalline compound. It is stable under neutral and acidic conditions but is extremely unstable under basic conditions, immediately releasing pNBOH. Furthermore, it was demonstrated that the pNB group could be smoothly deprotected in the presence of the side chain, without any rearrangement, to give **4**. Therefore, the pNB ester became the protecting group of choice.

2.2.1.1. Cross-coupling [7c]. Coupling between sp^3 and sp^2 carbons is more challenging than those between sp^2 and sp^2. In 1985, Kosugi and Migita reported hydroxymethylation by a cross-coupling reaction between aryl halides and Bu_3SnCH_2OH [11]. This method was applied to the TBDMS protected enol triflate. After optimization, the coupling product was isolated in 74%. Given the difficulty encountered with removing the TBDMS group downstream without significant degradation and the instability of the isolated enol triflate,



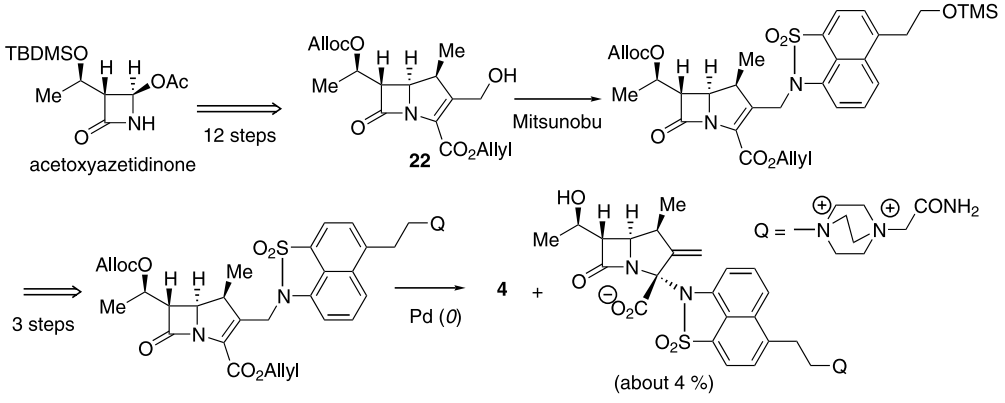
Scheme 4.

attention was focused on developing a one pot process starting with the TES diazo compound **13**. The issue was how to handle the base stable TES enol triflate **12** and the acid stable product **23**. If isolated **12** was used as starting material, the coupling reaction did not require halide sources (such as LiCl, $ZnCl_2$) [12]. However, $ZnCl_2$ was essential when in situ prepared **12** was used in order to maintain the reaction mixture at acidic pH where the product **23** was stable. The coupling reaction was carried out by addition of the cold basic solution of triflate **12** to the hot catalyst solution in the presence of $ZnCl_2$. Preparation of triflate **12** was modified for this coupling. When a mixture of TEA and diisopropylamine was used during triflation, reduction of triflate **12** was the main reaction pathway, yielding the 2-protio compound, because of α-hydride abstraction from the amines by the catalysts. Therefore, a mixture of tetramethylpiperidine and diisopropylethylamine was used for triflation which successfully suppressed the reduction to less than 5% during the coupling reaction. Under optimized conditions [$Pd(dba)_2$, trifurylphosphine, $ZnCl_2$, Bu_3SnCH_2OH, in HMPA at 70–80 °C under Ar], the product **23** was isolated in 45–55% after a quick silica gel column chromatography, followed by crystallization. Butyl transfer was also observed about 1/8 to 1/7 of hydroxymethyl transfer, even under the optimized conditions (Scheme 6). The hydroxymethyl carbapenem **23** was converted successfully to the candidate **4** via Tsuji–Trost allylic substitution [7f].

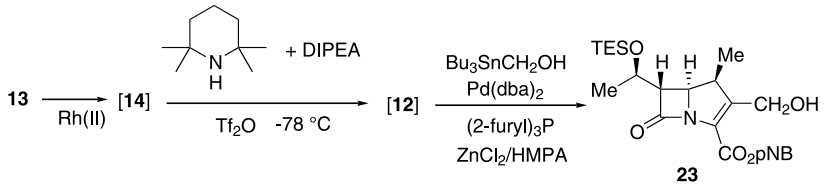
To bypass the difficulty associated with cross-couplings between sp^3 and sp^2 carbons, oxidative cleavage of 2-vinyl carbapenems, which were easily synthesized by Suzuki–Miyaura cross-coupling, was studied [7e]. Oxidative cleavage gave the surprisingly stable crystalline 2-formyl carbapenem in moderate yields. By reduction of the formyl group, the 2-hydroxy carbapenem pNB ester was obtained in high yield (Scheme 7). Due to difficulties in controlling the oxidation, this method was not pursued for further development.

2.2.2. *Coupling with the fully-functionalized side chain*

The ultimate goal for this project was development of a cross-coupling reaction between enol triflate **12** and the fully-functionalized side chain in one pot. There were many difficulties foreseen with this approach. First of all, there is no literature precedent for cross-coupling



Scheme 5.



Scheme 6.

between sp^2 carbons and sp^3 carbons bearing a nitrogen atom. Furthermore, the facile rearrangement of an α anion of *N*-alkyl substituted naphthosultam has been reported [13]. This fact implied that generation of an anion of *N*-methyl naphthosultam, which would have to be coupled, was impossible. Moreover, Suzuki–Miyaura cross-coupling was also considered improbable since the acidic naphthosultam ring would be expected to be released upon formation of a 9-BBN ate complex (Fig. 3).

In order to accomplish the cross-coupling reaction, the metal–carbon bond at the *N*-methyl position of naphthosultam must have covalent bond character. Therefore, tin was the metal of choice. Tributyltin–methylnaphthosultam was prepared from iodomethyltributyltin [14]. However, all attempts to cross-couple this reagent with enol triflate **12** failed.

The transmetalation step in the catalytic cycle was viewed as the problem in this case. If this were the case, a potential solution of the Stille–Migita approach would be lengthening of the Sn–CH_2 bond. Long Sn–C bonds were reported by Tzschach when he disclosed the preparation and properties of methylstannatrane [15]. In fact, this critical bond distance is 2.214 Å, which is ca. 0.1 Å longer than that in a typical alkylstannane. Vedejs capitalized on this characteristic when he demonstrated the palladium-catalyzed transfer of CH_3 and CH_2O-MOM to aryl halides [16]. However no other cross-coupling reports using this type of organostannane have appeared.

*2.2.2.1. Preparation of stannatrane chloride (**24**) [17].* Three methods for the preparation of chlorostannatrane have been reported. The first is a transmetalation between the Grignard reagent $N(CH_2CH_2CH_2MgCl)_3$ and $SnCl_4$ to provide **24** in 15% yield [18a]. The second method is the thermal redistribution of $N(CH_2CH_2CH_2SnMe_3)_3$ and Me_2SnCl_2 at 150–190 °C for 19 h, removing five equivalents of Me_3SnCl by vacuum distillation [18b]. This method is reported to

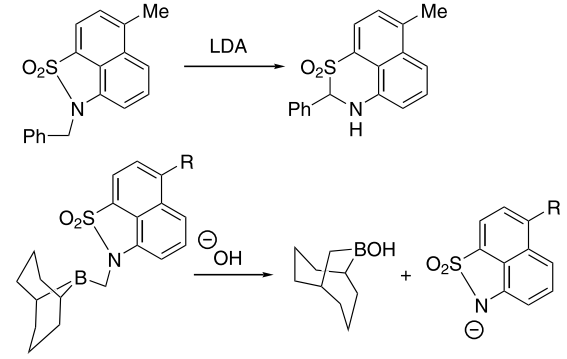
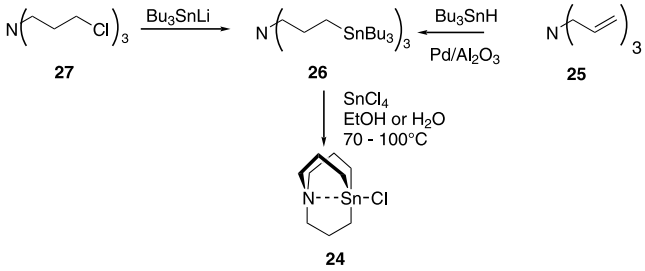


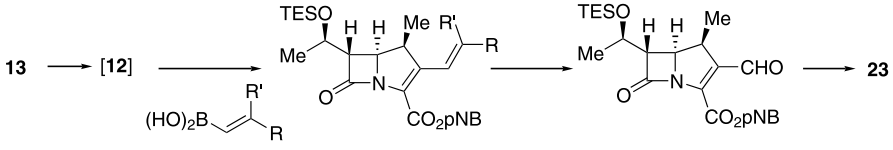
Fig. 3.

provide **24** in 40% yield; however, the hazardous reagents and conditions are not suitable for scale-up. Hydrozirconation of triallylamine **25** with three equivalents of Cp_2ZrHCl, followed by reaction with $SnCl_4$, affords **24** in 50% yield [16]. While this method works as reported, it is difficult to scale-up because of the high dilution required for the reaction to proceed. The cost of Cp_2ZrHCl is also a factor. We viewed the thermal redistribution approach as the most promising and investigated this method using $N(CH_2CH_2CH_2SnBu_3)_3$ **26**, which would be less hazardous than the corresponding $SnMe_3$ analogue.

Compound **26** was prepared in two ways (Scheme 8). Reaction between $N(CH_2CH_2CH_2Cl)_3$ **27** and Bu_3SnLi, itself prepared from Bu_3SnH and LDA, afforded **26** in



Scheme 8.



Scheme 7.

78% yield. Compound **26** was also prepared by the hydrostannylation of triallyamine **25** catalyzed by Pd/Al_2O_3 in 66% yield.

When the thermal redistribution of crude **26** (prepared from **27**) and $SnCl_4$ was attempted, formation of **24** was observed. Conversely, when **26** prepared from **25** was subjected to the same conditions, the reaction failed. Close comparison of **26** prepared by the different routes showed that the material from **27** was wet while that prepared from **25** was anhydrous. The addition of a small amount of water or an alcohol to anhydrous **26** promoted the desired transformation. With these conditions, the reaction proceeded smoothly at 70–100 °C to afford stannatrane chloride **24** in 50–55% isolated yield. We initially postulated that the promoter was HCl generated by reaction of the water or alcohol and $SnCl_4$. However, addition of dry HCl gas to an anhydrous reaction mixture did not facilitate the redistribution [19].

The effect of the addition of varying amounts of ethanol and water to the reaction was studied. The best yield was found when 0.5 equivalents of EtOH or 0.25 equivalents of water, based on $SnCl_4$, was added to the reaction.

During studies on the isolation of **24**, it was found that this compound's behavior is analogous to that of a carboxylic acid, residing primarily in the aqueous phase under basic conditions and in the organic phase under acidic conditions. This observation led to a simple extractive work-up sequence that easily removed the Bu_3SnCl produced in the thermal redistribution step and provided **24** as a crystalline compound. The tendency for **24** to dissolve in a basic aqueous phase also suggested a simple work-up method for Stille–Migita cross-coupling reactions that use cross-coupling reagents based on **24**. The tin by-products produced in such a reaction are easily removed by simple extraction with aqueous base. Stannatrane chloride **24** can then be recovered for future use by acidifying the aqueous phase with HCl and isolating the resulting crystals.

2.2.2.2. Preparation of cross-coupling partner. The synthesis of the fully-elaborated stannatrane coupling partner **33** is summarized in Scheme 9. Stannatrane chloride **24** was treated with the zinc reagent prepared by combining one equivalent of Et_2Zn and two equivalents of CH_2I_2 to provide iodomethylstannatrane **28** in quantitative yield. Treatment of **28** with naphthosultam **29** [13] in the presence of K_2CO_3 and DMF provided **30**, which was isolated as a crystalline solid from EtOAc. The alcohol was activated by conversion to triflate **31**. When **31** was treated with DABCO salt **32** at ambient temperature in acetonitrile, **33** was produced in high yield. This compound was isolated as an amorphous ditriflate salt by precipitation with ether. Alternatively, **33** could be prepared as a different salt form by simply changing the order of reactions. First combining the triflate of naphthosultam **29** with DABCO salt **32**, followed by coupling with iodomethyl **28**, provided **33** as the monoiodo monotriflate salt.

2.2.2.3. Stille–Migita cross-coupling with the fully-functionalized side chain. The preliminary single crystal X-ray diffraction data of **30** revealed that the Sn–N bond length is about 0.1 Å shorter than that of methyl stannatrane and the Sn–C bond is about 0.05 Å shorter [20]. This data corresponds well with the difference in electronegativity between the methyl and naphthosultam–methyl groups and encouraged us to pursue the cross-coupling.

With the coupling partners **12** and **33** in hand, the key cross-coupling reaction was explored (Scheme 10). The use of HMPA as solvent or cosolvent with DMPU, which was required for the cross-coupling of **12** with Bu_3SnCH_2OH, is not needed in this case. In fact, NMP was found to give superior yields. It is interesting to note that iodide acts as a poison for this coupling.

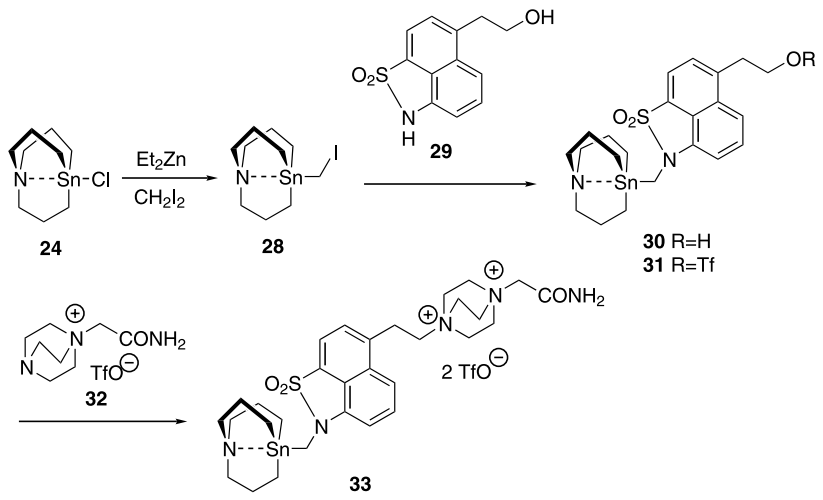
The preferred catalyst was prepared by combining $Pd_2(dba)_2 \cdot CHCl_3$ and tri-2-furylphosphine in warm NMP. This solution was added to a solution of coupling partners **12**, **33**, diisopropylethylamine and NMP. The tertiary amine was required to maintain basic conditions during the reaction. Decomposition was observed when the mixture was allowed to become acidic over the course of this cross-coupling. After 3 h at 60 °C, the assay yield of the product **34** was 98% (HPLC).

A workup procedure was devised that allowed the quantitative recovery of the stannatrane as chloride **24** as well as the isolation of the product **34** as a crystalline solid in high yield. The transmetallation step in the catalytic cycle returns the stannatrane as its triflate. This compound was converted to chloride **24** by diluting the crude reaction mixture with THF and washing with 20% aqueous NaCl. A solvent switch from THF to acetonitrile provided a slurry which, when filtered, gave 61% of the stannatrane as crystalline **24** and a clear mother liquor. When 2-propanol was added dropwise to this mother liquor, **34** crystallized and was isolated in 98% yield by filtration. This mother liquor was concentrated to dryness and the residue triturated with methanol to return the remaining 39% of stannatrane chloride **24**.

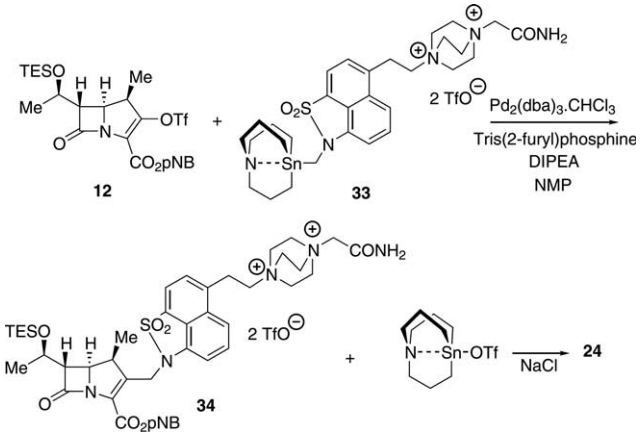
With this new cross-coupling method, the drug candidate **4** was prepared from the commercially available diazo compound **9** in only four steps in high yield and high efficiency.

3. Conclusion

As discussed here, cross-coupling methods allowed us to develop highly efficient and convergent processes. Especially in several carbapenem projects, drug candidates could be prepared by cross-coupling reactions with



Scheme 9.



Scheme 10.

fully elaborated side chains and a carbapenem triflate, which was prepared in two steps from a commercially available diazo compound. The cross-coupling reaction was accomplished not only in sp^2–sp^2 mode (Suzuki–Miyaura) but also in the more challenging sp^2–sp^3 mode (Stille–Migita) in the presence of various functional groups. This splendid functional group tolerability and mild reaction conditions open great possibilities for new, highly efficient processes for preparation and ultimately manufacture of drug candidates.

Acknowledgements

The author thanks many co-workers, whose names are cited in the references. He specifically thanks Drs David L. Hughes, Edward J.J. Grabowski, Ronald W. Ratcliffe, Frank P. DiNinno, Lovji D. Cama and Milton L. Hammond for helpful discussions and suggestions for this review.

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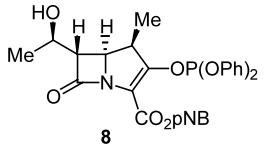

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[19] The author thanks Professor John Brown for helpful discussions on this issue. This promotion may be due to nucleophilic attack of oxy-nucleophiles to Sn to stimulate redistribution.
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