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Nine Times Fluoride can be Good for your Syntheses. Not just Cheaper: Nonafluorobutanesulfonates as Intermediates for Transition Metal-Catalyzed Reactions

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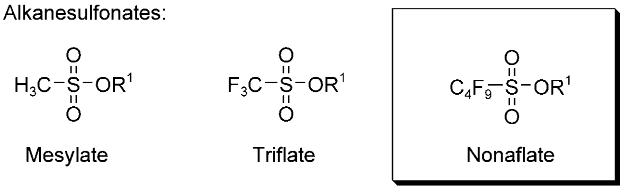
Abstract: How much fluoride is good for a strong electron-withdrawing effect? In this review we summarize recent results on the use of perfluoroalkanesulfonates, in particular of the cost effective nonafluorobutanesulfonates (nonaflates), in transition metal-catalyzed reactions and a few other typical transformations. During the last decade many advantages over the commonly used triflates have been discovered. The generation of alkenyl and (het)aryl nonaflates and their applications in metal-catalyzed processes such as Heck, Suzuki, Sonogashira, Stille, and Negishi couplings or amination reactions are described. Although far from a systematic investigation, all the presented results clearly demonstrate the many advantages of nonaflates and of similar higher fluorinated sulfonates in laboratory and industrial scale organic synthesis.

Keywords: arylation; catalysis; C–C coupling; olefination; palladium; perfluorinated substituents

1 Introduction

Sulfonylating reagents are of great importance in organic synthesis. The simple preparation of sulfonates is achieved by trapping nucleophiles such as alkoxides or enolates with suitable sulfonylating agents (Scheme 1). Mesylates or tosylates are frequently used intermediates, but for a variety of synthetic applications perfluoroalkanesulfonates are particularly useful as their strongly electron-withdrawing perfluorinated alkyl chain dramatically enhances the reactivity.



Scheme 1. (Perfluoro)alkanesulfonates commonly used in synthesis.

Hydroxy groups are frequently converted into sulfonates because of two reasons: a) the sulfonate ion (RSO_3^-) is an excellent leaving group, and b) the strong electron-withdrawing effect of the perfluoroalkyl chain reduces the electron density at the adjacent carbon atom considerably. This makes sulfonates not only ideal substrates for many nucleophilic displacement reactions, but it also allows for a smooth transition metal insertion into the carbon-oxygen bond. Consequently, sulfonates are very valuable and versatile alternatives to halides in metal-catalyzed coupling reactions (Scheme 2).

Among the perfluoroalkanesulfonates the triflates (CF_3SO_2O-) are the most popular derivatives and have been studied in countless applications. At the time of Hanack's review[1] on perfluoroalkanesulfonates most known reactions dealt with triflates. Later Ritter summarized synthesis and use of alkenyl and aryl triflates.[2] Very commonly perfluoroalkanesulfonates can be found as silyl sulfonates that are used for different purposes. Their synthetic applications have been reviewed by Simchen[3a] and Vorbrüggen.[3b]

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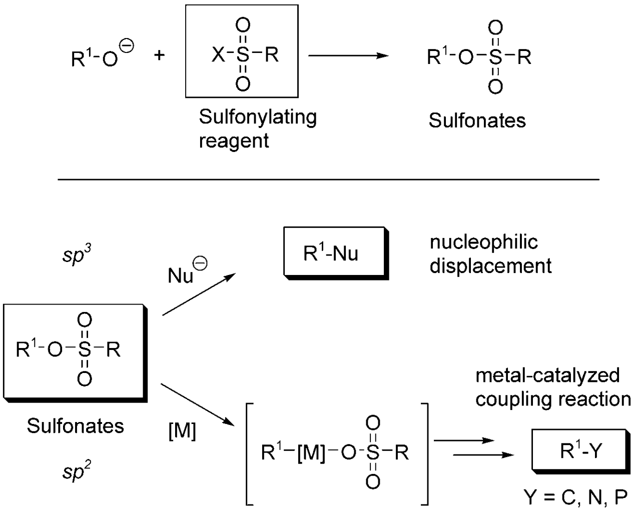
Hans-Ulrich Reissig was born in Helmbrechts, Germany, in 1949. He studied chemistry at the Ludwig-Maximilians-Universität München, where he received the diploma in 1975 and the doctoral degree in 1978, working under the direction of Rolf Huisgen. For postdoctoral studies he spent one year with Edward Piers at the University of British Columbia, Vancouver, and afterwards started independent research at the Universität Würzburg (mentor Siegfried Hünig). After his habilitation in 1984 he was appointed Privatdozent and awarded Heisenberg and Winnacker Fellowships. In 1986, he joined the Technische Hochschule Darmstadt as associate professor and from 1993 to 1999 he held a chair of organic chemistry at the Technische Universität Dresden. He has been full professor at the Freie Universität Berlin since 1999. He is interested in many areas of synthetic organic chemistry, including cyclopropanes, allenes, heterocyclic chemistry, metal-promoted reactions and synthesis of natural products and their analogues.

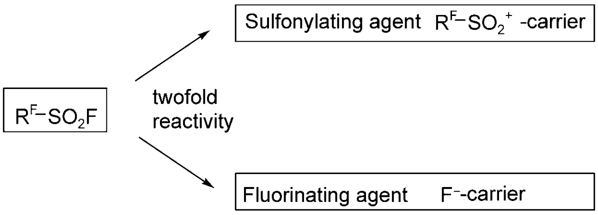


Scheme 2. Possible reactions of alkane-, alkene- and arenesulfonates.

Nonaflates (nonafluorobutanesulfonates, NfO^-), which are the C_4 homologues of triflates, did not receive so much attention until recently. However, during the last years many very useful applications of nonaflates have been published emphasizing their tremendous synthetic advantages. In this review we therefore summarize new developments in synthetic applications of nonaflates and related compounds emphasizing metal-catalyzed reactions.

Nonafluorobutanesulfonyl fluoride (nonaflyl fluoride, $C_4F_9SO_2F$, **NfF**) is the most widely used commercially available reagent for the synthesis of nonaflates. Early applications of this reagent have been reviewed.[4] **NfF** is prepared on the industrial scale by anodic fluorination of a cyclic sulfolene precursor.[5] Nowadays **NfF** is a bulk product and commercially available. It is remarkable that **NfF** is cheaper than any of the common reagents for triflating reactions. The reagent is bench stable and storable for years.

The two-fold reactivity of **NfF** is of great interest for its synthetic applications (Scheme 3). As a sulfonylating reagent it can be used as a transfer agent for the nonaflyl group. In addition, it can be employed as a fluoride anion carrier for the nucleophilic introduc-



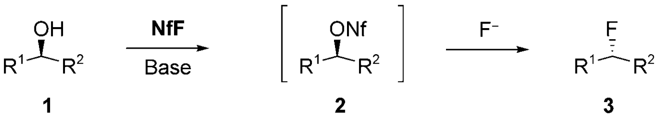
Scheme 3. Reactivity of nonafluorobutanesulfonyl fluoride (**NfF**).

tion of fluorine. Although this very useful chemistry has recently been reviewed by Vorbrüggen[6] a few applications will be presented in section 2.

In general hydroxy groups connected to alkyl, alkenyl and aryl groups can react with nonaflating agents to create the corresponding nonaflates. In the following sections we summarize the reactions for the synthesis and use of alkyl (section 2), alkenyl (section 3), and aryl nonaflates (section 4). Miscellaneous reactions of nonaflates and related species are treated in section 5.

2 Alkyl Nonaflates

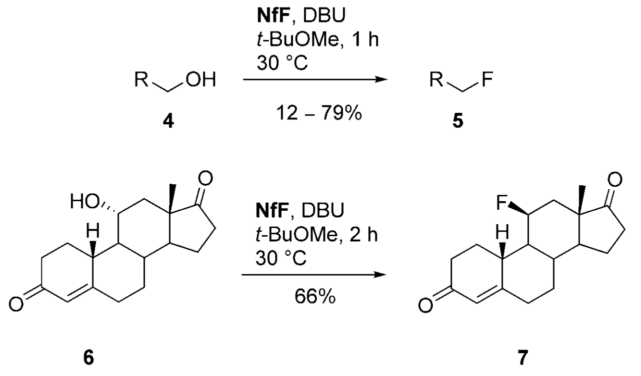
Fluorinated compounds have received much attention as potential pharmacologically active compounds and hence mild fluorination methods are of extreme importance. The strong electron-withdrawing property of the nonafluorobutyl chain in combination with the SO_2 moiety is an ideal tool for creating a good leaving group. The reagent **NfF** additionally provides a fluoride anion and can therefore elegantly be used as fluorination reagent for alcohols (Scheme 4). With **NfF** alcohols **1** are converted into alkyl nonaflates **2** that can directly react under S_N2 displacement with *in situ* generated fluoride to give the corresponding fluorinated products **3** under inversion of configuration.



Scheme 4. Nucleophilic fluorination of alcohols *via* alkyl nonaflates employing **NfF** as reagent.

This transformation was carefully studied by Vorbrüggen et al. who demonstrated that **NfF** in the presence of DMAP served as an excellent fluorinating agent for primary alcohols. However, with secondary alcohols the formation of a mixture of the fluoroalkane, the corresponding olefin and the *N*-alkyl-4-dialkylaminopyridinium nonaflate salts was observed.[7] The method was strongly improved using a combination of DBU and **NfF** allowing the conversion of primary alcohols **4** and secondary alcohols **6** into the corresponding alkyl fluorides (Scheme 5).[8] This method was applied to the synthesis of fluorinated derivatives of androst-5-enes and pregnenes[9] as well as to the preparation of fluorinated progestins for breast tumor imaging and radiotherapy.[10]

This simple and highly efficient method was successfully used for the preparation of fluorinated nucleosides.[11,12] The synthesis of lodenosine demonstrates the applicability on the industrial scale.[12c] A closely related method for the fluorination of primary, secondary and even tertiary alcohols was disclosed by Yin and co-workers.[13] This group demonstrated that a combination of **NfF**, $NR_3(HF)_3$ and NR_3 can efficiently be employed for this type of conversion furnishing the corresponding alkyl fluorides in very good yields.



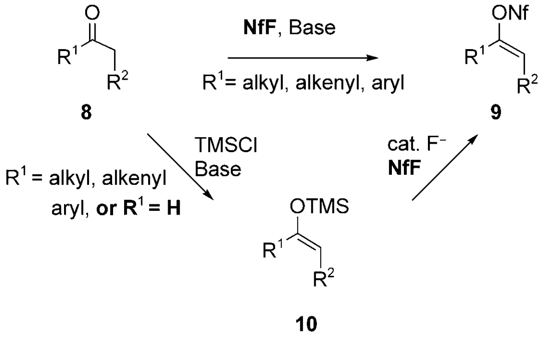
Scheme 5. Vorbrüggen method for the synthesis of alkyl fluorides employing **NfF**.

The excellent leaving group characteristic of alkyl nonaflates was also exploited by Klar and Vorbrüggen to prepare epoxides from diols. The combination of DBU and **NfF** allowed this direct conversion in good yields.[14] Another example was reported by Kemp and his group. For an S_N2 displacement of hydroxy groups of penicillin and cephalosporine derivatives they included an example of a nonaflate that was displaced with iodide in good yield.[15] Although the number of examples for the application of alkyl nonaflates present in the literature is still limited it is evident that these intermediates have a high potential for laboratory and industrial processes.

3 Alkenyl Nonaflates

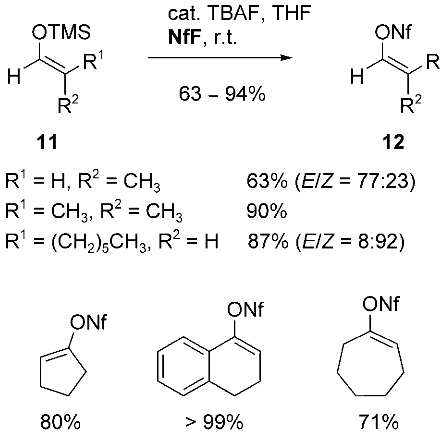
Nonaflyl fluoride is also an excellent reagent for the conversion of carbonyl compounds into alkenyl nonaflates. Their applications in metal-catalyzed coupling reactions are summarized in the two major sections of this review. From a synthetic point of view the transformation of a carbonyl function into an alkenyl sulfonate is of vital importance since these intermediates are very frequently used in metal-promoted reactions. Although alkenyl bromides and iodides are commonly and efficiently employed in metal-catalyzed couplings they are not always easily available. The introduction of halogen substituents during a complex synthesis can be tedious and unselective. The transformation of a carbonyl group into an alkenyl sulfonate, however, can be achieved with fairly simple and highly selective methods.

In general the synthesis of alkenyl sulfonates is achieved by deprotonation with a suitable base and subsequent addition of an appropriate sulfonylating reagent (Scheme 6, **8** to **9**). The trapping of an *in situ* generated enolate can be problematic in some cases: in particular aldehyde-derived sulfonyl enol ethers can usually not be synthesized by simple deprotonation and quenching. The early work of Reissig and Hünig opens an easy access to these alkenyl sulfonates.[16] They discovered, that these compounds can easily be prepared from the corresponding trimethylsilyl enol ethers **10** and **NfF** by using a catalytic amount of fluoride to initiate the reaction. As **NfF** corresponds to a fluoride source it is able to keep the catalytic cycle ongoing. Detailed investigations revealed that the counter-ion of the fluoride catalyst has a crucial influence on the selectivity of O- and C-sulfonylation. "Bigger" counter-ions such as cesium or tetraalkylammonium ions were preferably used for the selective synthesis of alkenyl nonaflates.



Scheme 6. Fluoride-catalyzed synthesis of alkenyl nonaflates *via* trimethylsilyl enol ethers employing **NfF**.

This work was the origin for a broad exploration of our group in the synthetic use of alkenyl nonaflates. It allows for the conversion of ketones and aldehydes into alkenyl nonaflates *via* TMS-enol ethers **10** using **NfF** and catalytic amounts of tetrabutylammonium fluoride (TBAF) (Scheme 6). Specific examples are depicted in Scheme 7.[17] Under these conditions several alkenyl nonaflates **12** were synthesized from aldehyde-derived TMS-enol ethers **11**. The method was further extended to a variety of compounds testing different fluoride sources that led to the development of a method using either TBAF or a combination of TBAF and KF as promoters.[18] Alkenyl nonaflates **12** were synthesized in up to 90% yields. Alkenyl nonaflates derived from acyclic and cyclic ketones were also available in up to 99% yield. The "detour" *via* trimethylsilyl enol ethers permits that all advantages of their regio- or stereoselective generation are transferred to the resulting alkenyl nonaflates.



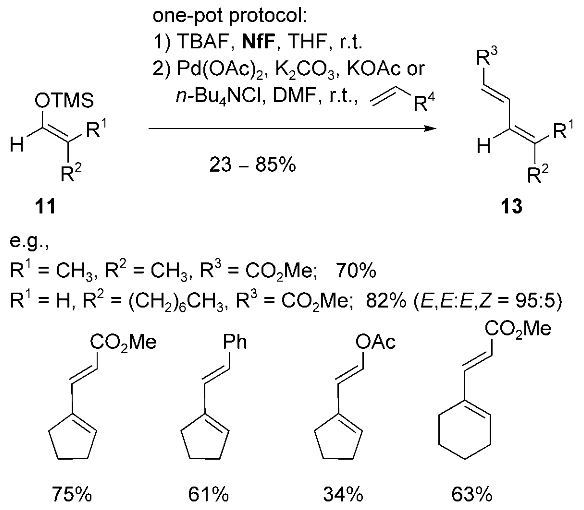
Scheme 7. Synthesis of alkenyl nonaflates *via* TMS-enol ethers employing **NfF** and catalytic amounts (0.15–0.29 equiv.) of fluoride.

Ketone-derived alkenyl nonaflates can also be prepared by direct base treatment and trapping of the enolate with a suitable nonaflating reagent (e.g., NfF or NfONf).[18b] Recently Lyapkalo et al. published an interesting general method for the synthesis of alkenyl nonaflates using phosphazene bases.[19]

In the case of C_S-symmetrical prochiral ketones the synthesis of alkenyl nonaflates offers an excellent option to desymmetrize ketones by deprotonation. This was proved by showing that the nonaflate derived from 4-*tert*-butylcyclohexanone is available in fair yield and with good enantiomeric excess using a chiral base for deprotonation.[20] Similarly, the TMS-enol ether was enantioselectively prepared and then transformed by fluoride catalysis into the nonaflate utilizing the above-mentioned method. It proceeded without degradation of the enantiomeric excess of the starting silyl enol ether.[20]

Since alkenyl nonaflates are readily available with these methods several examples of palladium-catalyzed coupling reactions have been explored. Our group provided the first investigations on Heck reactions. Alkenyl nonaflates were successfully coupled in the presence of palladium(II) acetate giving the expected 1,3-dienes. Further exploration of the method finally led to the development of a one-pot procedure for the synthesis of 1,3-dienes **13** starting from TMS-enol ethers **11** (Scheme 8).[17,21] The Heck reactions were also carried out with alkenyl nonaflates directly generated from ketones finally giving 1,3-dienes in good yields. Recently, Lyapkalo et al. published an interesting room temperature protocol for Heck reactions of alkenyl nonaflates. They discovered that this transformation can be carried out using only $Pd(OAc)_2$, a base and DMF thus allowing for very mild conditions in the coupling step.[22]

Bicyclic alkenyl nonaflates **14** derived from tropinone, oxa- or thia-analogues were successfully con-



Scheme 8. One pot syntheses of 1,3-dienes **13** from TMS-enol ethers and **NfF** *via* alkenyl nonaflates and subsequent Heck reaction.

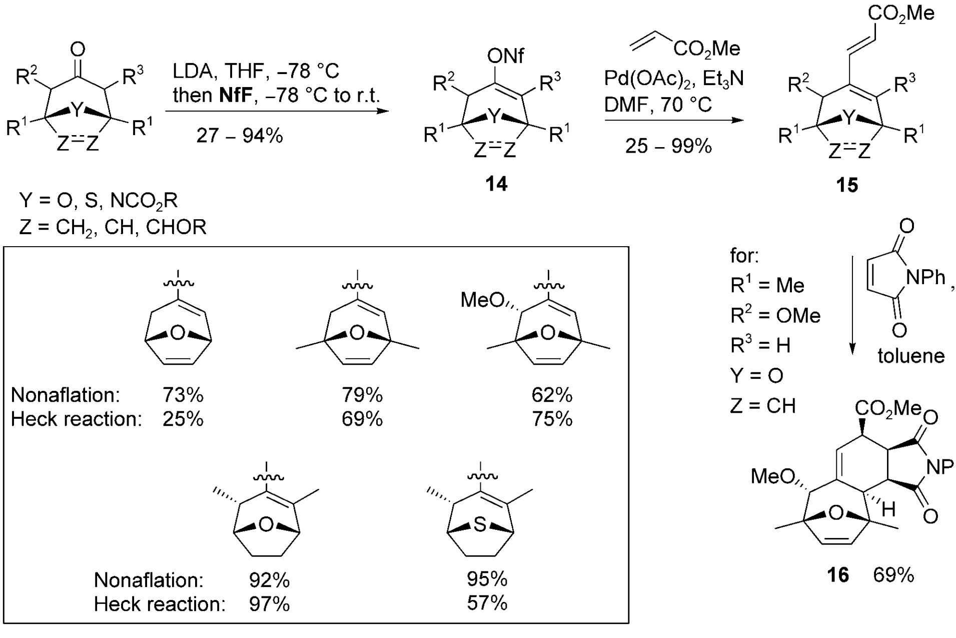
verted into the corresponding coupling products using Heck and Sonogashira reactions (Scheme 9). The resulting 1,3-dienes **15** were transformed by Diels–Alder reactions creating highly substituted new tetracyclic skeletons **16** in stereoselective fashion.[23,24]

Further exploration of bicyclic alkenyl nonaflates **14** led to the development of efficient protocols for Suzuki reactions leading to **17**[25] or Sonogashira reactions[26] furnishing **18** (Scheme 10). Under conditions originally reported by Miyaura for alkenyl triflates[27] the bicyclic alkenyl nonaflates were coupled with bispinacolatodiboron to provide bicyclic alkenyl boronic esters. This method was successfully applied to the preparation of an epibatidine-atropine hybrid.[28]

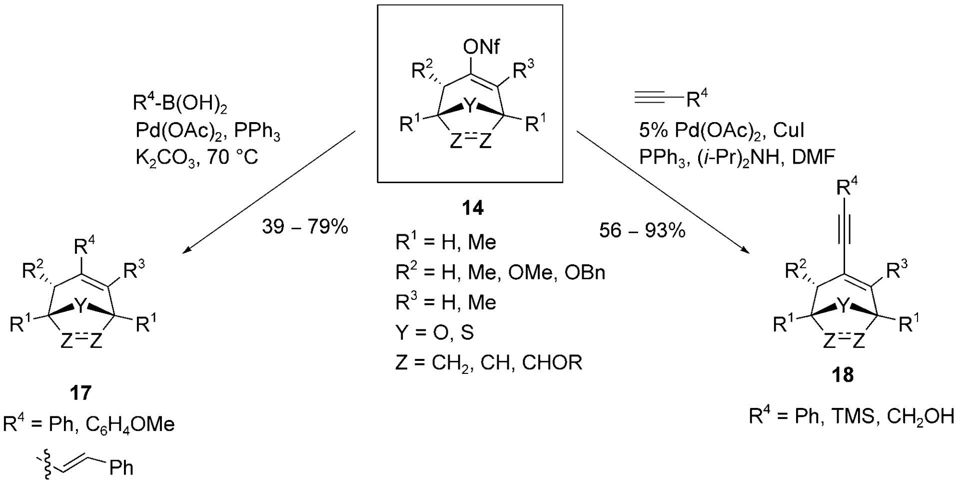
An intriguing one-pot procedure for the synthesis of conjugated enynes based on readily available carbonyl compounds involving a Sonogashira reaction was recently disclosed by Lyapkalo et al.[29a] Enolizable ketones or aldehydes were transformed *in situ* into the corresponding alkenyl nonaflates **19** by treating them with a first equivalent of phosphazene P1 or P2 base (Scheme 11). Upon exposure to a second equivalent of this strong base elimination gave the corresponding alkyne **20**[29b] that can then readily react in a Sonogashira reaction with a second alkenyl nonaflate **21** created from a cyclic precursor ketone efficiently providing the desired enynes **22**.

It was early demonstrated by de Meijere's group that alkenyl nonaflates can smoothly be employed in Heck reactions. During the exploration of the reactivity of methylenecyclopropanes this group reported one example of a successful coupling of these interesting olefins with cyclohexenyl nonaflate.[30] Further studies on the synthetic potential of alkenyl nonaflates **23** led to their use in a double Heck reaction creating 1,3,5-hexatrienes such as **25a**.[31] These 1,3,5-triene building blocks can undergo a subsequent electrocyclization and aromatization generating compounds of type **26** (Scheme 12). This group also exploited the higher reactivity of alkenyl nonaflates compared to alkenyl chlorides for the introduction of two different alkenes allowing the preparation of triene **25b**.

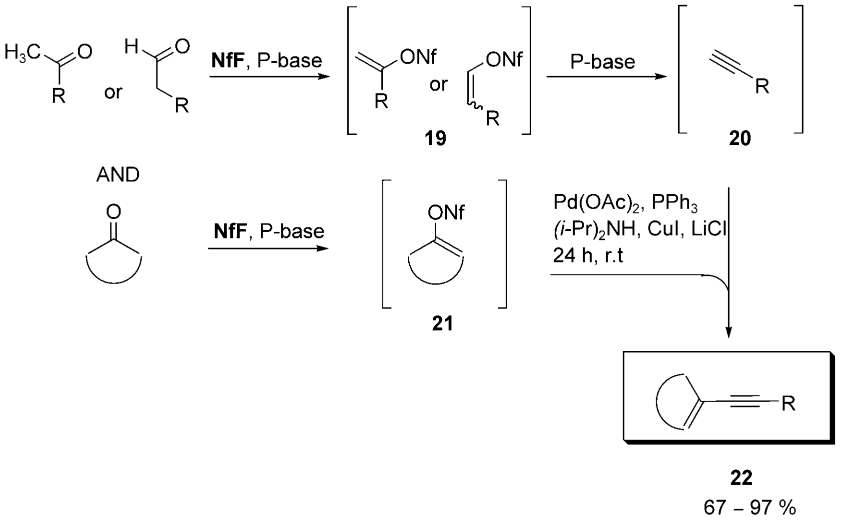
Wada and co-workers explored cross-couplings of dienyl nonaflates (Scheme 13).[32] They were able to



Scheme 9. Synthesis and Heck reactions of bicyclic alkenyl nonaflates **14** derived from 8-heterobicyclo[3.2.1]octanone derivatives followed by Diels–Alder reaction to tetracyclic compounds **16**.



Scheme 10. Suzuki and Sonogashira reactions of bicyclic alkenyl nonaflates **14** leading to compounds **17** or enynes **18**.

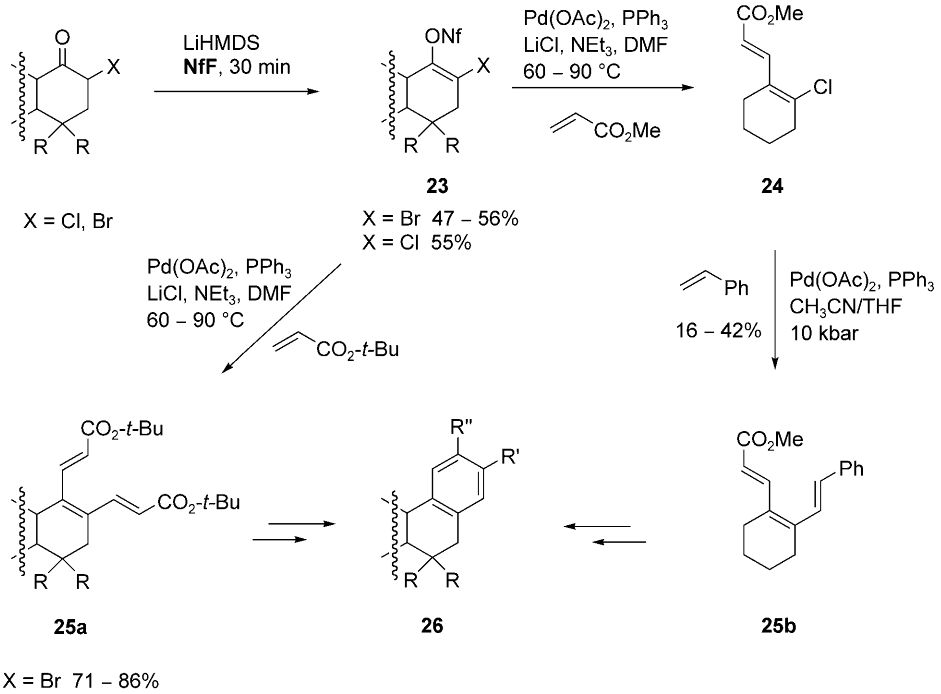


Scheme 11. One-pot protocol for the *in situ* synthesis of alkynes **20** and their couplings to alkenyl nonaflates **21** furnishing enynes **22**.

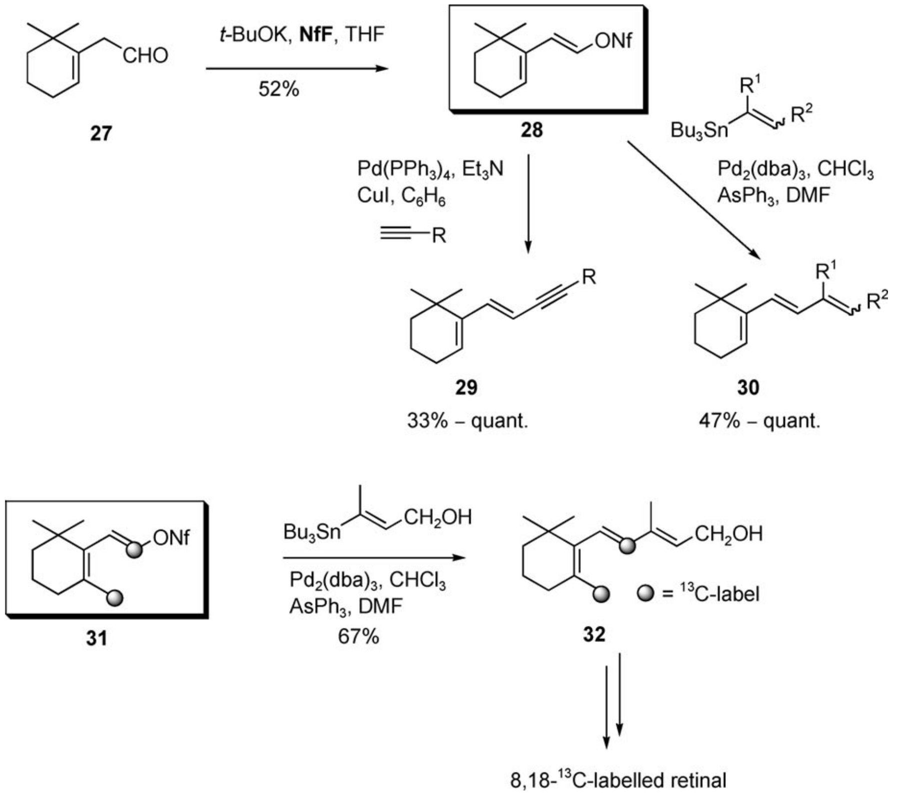
develop efficient protocols for Sonogashira and Stille reactions giving products **29** and **30** in good to excellent yields. The required nonaflate **28** was prepared from aldehyde **27** using *t*-BuOK and **NfF**. They also applied triflates and stated that not only the high costs of triflating reagents but also the troublesome preparation of several triflates in their opinion strongly favours nonaflates for synthetic applications. They demonstrated the efficacy of their method during the synthesis of a ^{13}C-labelled retinal.[33] Labelled nonaflate **31** was converted into triene **32** that was further transformed. Brückner et al. also used alkenyl nonaflates and different alkenes in efficient Sonogashira couplings.[34]

In the syntheses of guanacastepenes A and E, Sorensen has shown that alkenyl nonaflates can efficiently be converted into the corresponding stannane reagents with hexamethyldistannane as the tin source.[35] Again nonaflates showed superior reactivity compared to the corresponding triflates.

Similar to Heck, Sonogashira, and Suzuki reactions cross-couplings with zinc- or copper-derived organometallics were successfully explored. Cross-couplings of alkenyl nonaflates derived from β-keto esters, β-diketones, and α-diketones with organozinc halides were reported by Rossi and Bellina.[36] The required alkenyl nonaflates were synthesized by using NaH and **NfF** and they were then coupled with alkyl-, alkynyl-, and arylzinc chlorides furnishing the desired products in good to excellent yields. Dieter et al. reported on the reactions of alkyl cuprates with alkenyl halides and triflates.[37] In these publications they enclosed one example of an alkenyl nonaflate that was successfully coupled with an *N*-Boc-pyrrolidine-de-



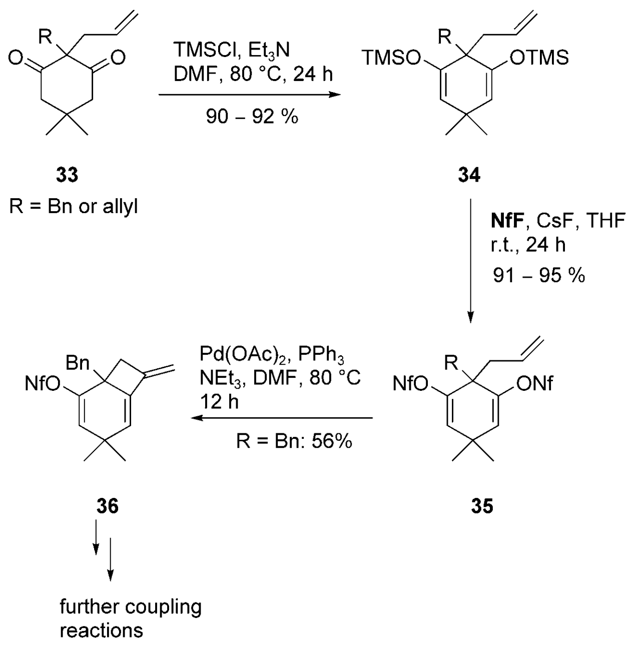
Scheme 12. Synthesis of 1,3,5-trienes **25** and benzene derivatives **26** *via* alkenyl nonaflates **23**.



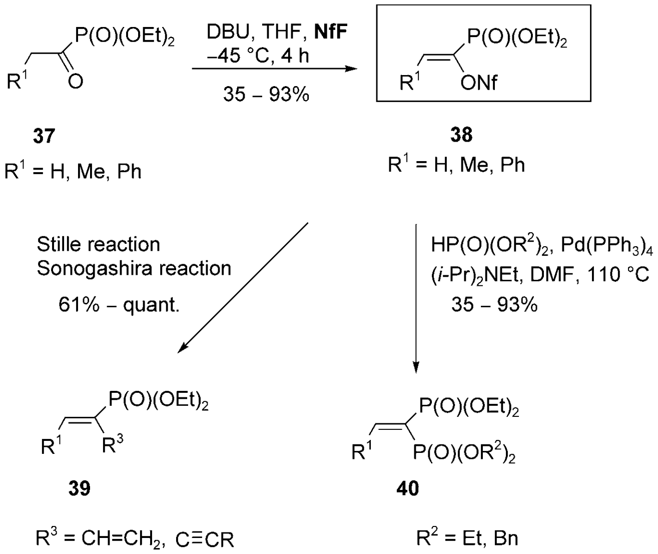
Scheme 13. Sonogashira and Stille reactions of dienyl nonaflates and their use in the synthesis of ^{13}C-labelled retinal.

rived cuprate. Not surprisingly, the nonaflate gave better yields than the corresponding triflate. Similarly, Knochel recently showed that alkenyl nonaflates can nicely be coupled with alkyl cuprates under iron catalysis.[38]

The first synthesis and coupling reaction of bisnonaflates prepared from dimedone derivatives **33** was



Scheme 14. Synthesis and coupling reactions of bis-alkenyl nonaflates **35** leading to bicyclic compound **36**.



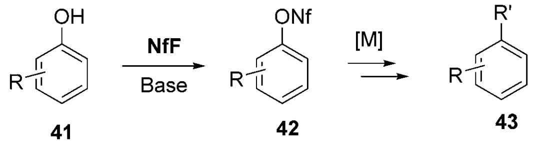
Scheme 15. Synthesis and reactions of phosphoalkenyl nonaflates **38**.

reported by Bräse (Scheme 14).[39] The bisnonaflates **35** were synthesized from **34** using the Reissig–Hünig method with CsF as fluoride source. Subsequent intramolecular Heck reaction involves a 4-*exo-trig* cyclization leading to the interesting highly strained product **36**. This group also included an example of a Sonogashira reaction.

Minami et al. focussed on the synthesis of phosphoalkenyl nonaflates **38** (Scheme 15)[40] which were synthesized from **37** by applying DBU and **NfF**. Nonaflates **38** were then used in Stille and Sonogashira reactions leading to products **39**. A subsequent report also shows a C–P coupling reaction under palladium catalysis giving geminal (bis)phosphoalkenyl compounds **40**.[41]

4 Aryl and Hetaryl Nonaflates

Similarly to alkenyl nonaflates the related aryl compounds **42** have been generated and successfully used in metal-catalyzed couplings. These nonaflates are readily available from phenols **41** by base treatment and quenching with **NfF** (Scheme 16). Typical examples of numerous synthetic applications of aryl nonaflates leading to coupling products **43** are discussed in this section.



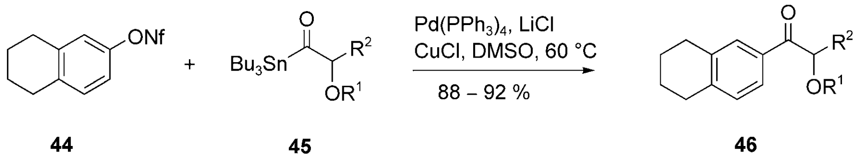
Scheme 16. Generation of aryl nonaflates **42** and coupling to **43**.

The Stille coupling of aryl nonaflates has been studied by Corey and co-workers[42] who employed CuCl/LiCl to promote the reactions of aryl nonaflates **44** with sterically demanding stannanes **45** leading to aryl ketones **46** (Scheme 17). Corey states that the nonaflates are similar in reactivity but less prone to O–SO_2 bond cleavage processes compared to the corresponding triflates.

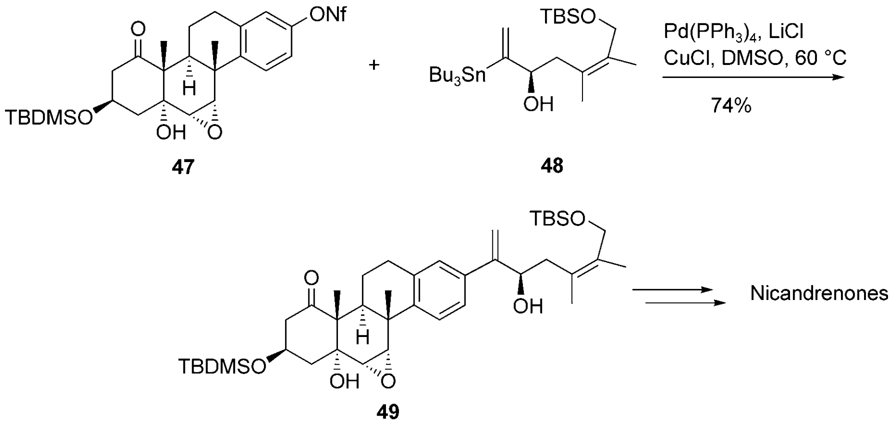
This Stille coupling protocol was successfully applied to the total synthesis of nicandrenones.[43] Vinylstannane **48** was coupled to polycyclic aryl nonaflate **47** which was generated from the corresponding phenol with triethylamine and **NfF** (Scheme 18). Subsequent reactions of product **49** led to nicandrenones.

Aryl nonaflates have successfully been used in Sonogashira reactions as disclosed by Maleczka et al. who demonstrated that CsF in the presence of PMHS (polymethylhydrosiloxane) facilitates the coupling with several alkynes (Scheme 19).[44] Aryl nonaflates **50** were coupled with alkynes **51** furnishing the expected products **52** in good to excellent yields. This group also included one example of a cyclic alkenyl nonaflate giving a cyclohexenyne in 82% yield.

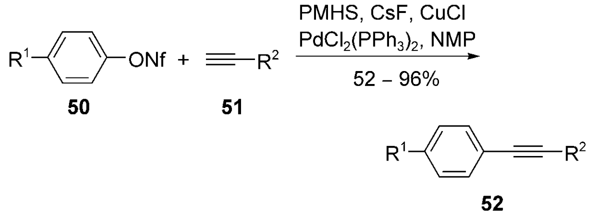
An aryl nonaflate coupling with an alkyne was reported by Swager et al.[45] in their approach to new poly(phenylene ethynylenes). A bisnonaflate was generated with triethylamine and then coupled with TMS-acetylene giving the desired product in excellent yield. Aryl nonaflates can also be coupled under Pd catalysis with alkynes in the presence of the bulky Cp*Li (pentamethylcyclopentadienide lithium) as



Scheme 17. Aryl nonaflates **44** in LiCl/CuCl promoted Stille couplings with acylstannanes **45** leading to aryl ketones **46**.



Scheme 18. Synthesis of a nicandrenone precursor **49** by Stille coupling of aryl nonaflate **47** with vinylstannane **48**.



Scheme 19. PMHS-mediated Sonogashira reactions of aryl nonaflates **50** to arylalkynes **52**.

base. Again nonaflates gave much better results than the corresponding triflates.[46]

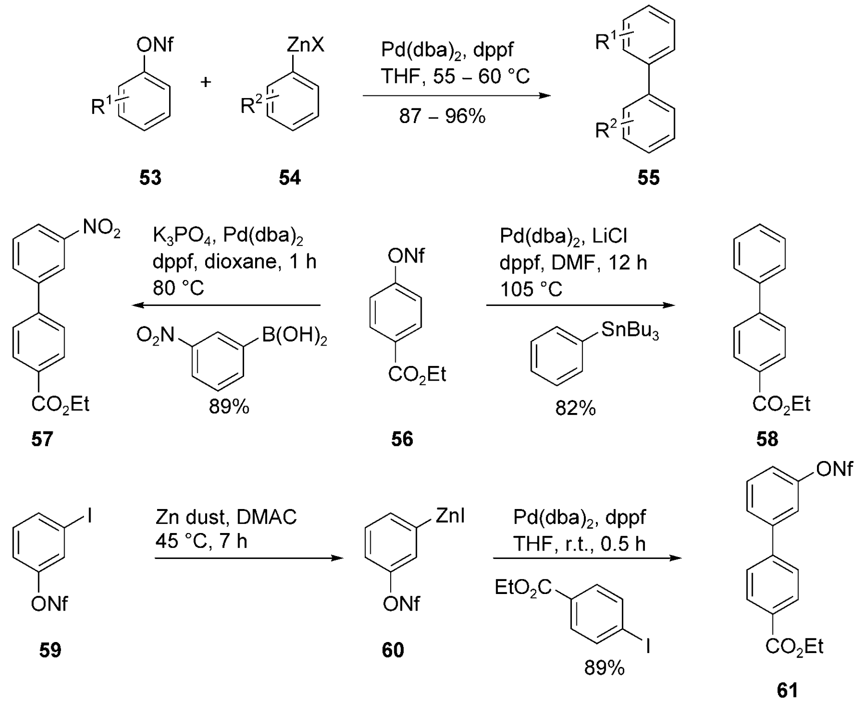
Negishi couplings of arylzinc compounds with aryl nonaflates were thoroughly investigated by Knochel and his group.[47] Arylzinc compounds **54** were reacted with aryl nonaflates **53** giving the desired coupling products **55** in very good yields (Scheme 20). This group also included an example of a high-yielding Suzuki coupling of functionalized aryl nonaflate **56** to give product **57**. The Stille reaction of this aryl nonaflate provided compound **58** with similar efficacy. Further experiments showed that iodoaryl nonaflate **59** can smoothly be converted into the corresponding arylzinc compound **60** which was then coupled under palladium catalysis without affecting the nonaflate moiety to give biaryl product **61** in 89% yield. A competition reaction of an aryl nonaflate and the corresponding aryl triflate with 4-chlorophenylzinc bromide shows that the nonaflate reacts approximately 1.4 times faster than the triflate. This result of Knochel et al. clearly demonstrates that nonaflates are not only superior in stability during synthesis and handling, but are generally slightly more reactive in palladium-catalyzed reactions.

Further investigations of the Knochel group showed that alkylzinc iodides can be successfully coupled with aryl iodides and nonaflates under nickel catalysis.[48] This method was later extended to arylzinc halides using a nickel dichloride-diethyl phosphite catalyst system.[49] Alkynylzinc reagents can be used as alternative to alkynes in palladium-catalyzed couplings to form aryl-alkynyl bonds. Rossi demonstrated that aryl nonaflates are excellent coupling partners in this type of reaction.[50]

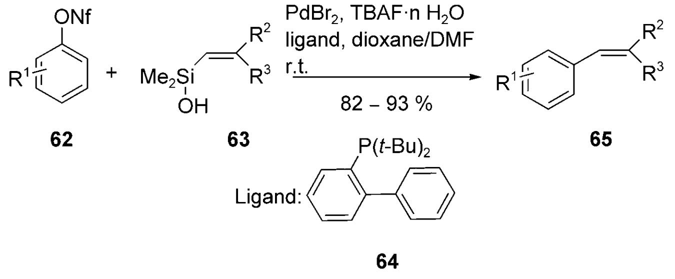
Coupling reactions of alkenylsilanols with nonaflates were introduced by Denmark (Scheme 21). Under palladium catalysis employing ligand **64** different aryl nonaflates **62** were converted into products **65** by coupling with alkenylsilanols **63**.[51]

Other examples of C–C coupling reactions were disclosed by Reiser who used aryl nonaflates in Heck reactions with 2,3-dihydrofuran at high pressure.[52] An aryl nonaflate as component for reductive hydrophenylation was described by Kaufmann.[53]

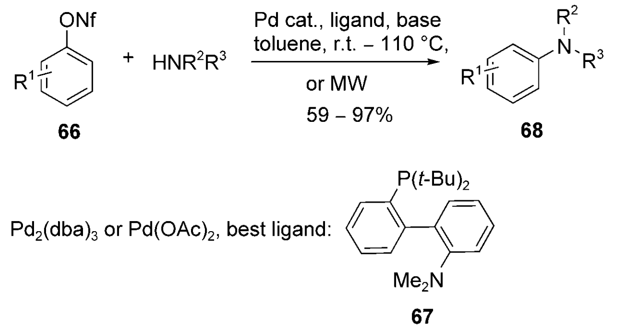
Similarly to C–C coupling reactions, aryl nonaflates were also employed in C–N bond formations. Whereas Thang and Sui reported one example[54] Buchwald and his group systematically investigated the use of aryl nonaflates (Scheme 22).[55] Aryl nonaflates **66** were coupled in the presence of ligand **67** to give the corresponding aniline derivatives **68** in good yields.



Scheme 20. Palladium-catalyzed couplings of arylzinc compounds with aryl nonaflates.



Scheme 21. Coupling of aryl nonaflates **62** with alkenylsilanols **63**.



Scheme 22. Aryl nonaflates **66** in C–N coupling reactions leading to aniline derivatives **68**.

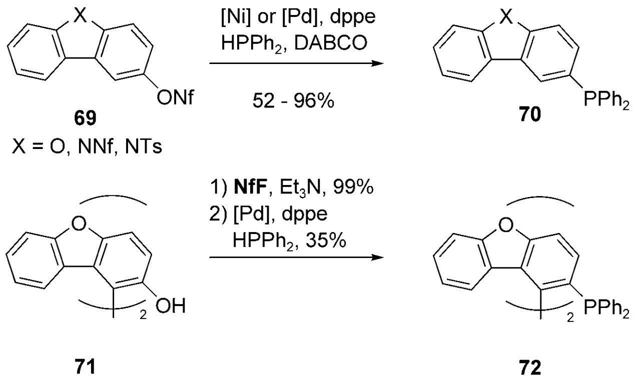
These reactions were considerably accelerated by microwave irradiation.[56,57]

Palladium-catalyzed C–N couplings of aryl nonaflates were also utilized in the synthesis of estrieno[2,3-*b*]pyrroles and estrieno[3,4-*b*]pyrroles[54] as well as in the synthesis of new cyclo-NOBIN ligands.[58] Bolm et al. coupled aryl nonaflates with sulfoximines under palladium or nickel catalysis to yield *N*-arylsulfoximines.[59] The reaction of a bromoaryl nonaflate with *n*-butyllithium led to an aryne intermediate which was regioselectively trapped by the lithium salt of a secondary amine to provide an aminated benzene derivative. The product was required for the synthesis of oxaza-adamantyl cannabinoids.[60]

Several examples of C–P and C–As coupling reactions utilizing aryl nonaflates are known. Hiemstra and his group prepared a series of dibenzofuran- or carbazole-based diphosphine ligands **70** or **72** by palladium- or nickel-catalyzed couplings of nonaflates **69** or **71** (Scheme 23).[61]

In an attempted synthesis of P,N ligands the coupling of binaphthyl-derived aryl nonaflate **73** with morpholine failed to give product **74** (Scheme 24).[62] An alternative Staudinger approach was developed allowing introduction of the amino group *via* different azides. They form iminophosphorane **76** which rearranges to an aminophosphonium salt finally affording the desired product **77**.

The group of Chan reported the synthesis of arylphosphines or arylarsines by palladium-catalyzed phosphination and arsination including examples with nonaflates.[63,64] Another palladium and copper co-catalyzed C–P coupling reaction was examined by Livinghouse et al. who showed that Ph(Me)PH·BH_3 could be coupled in good yields to aryl halides and

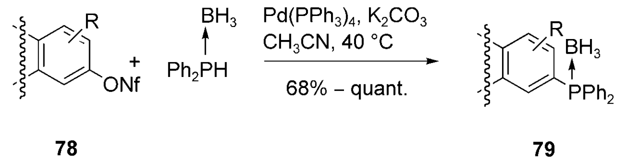


Scheme 23. C–P coupling reactions of dibenzofuran- or carbazole-derived aryl nonaflates.

phenyl nonaflate.[65] The reaction of $Ph_2PH{\cdot}BH_3$ with aryl nonaflates **78** was studied by Lipshutz et al. Under palladium catalysis aryl nonaflates were converted into the BH_3-stabilized triarylphosphines **79** (Scheme 25).[66] Masuda and his group investigated the coupling of pinacolborane with different aryl halides and triflates. They included one example of an aryl nonaflate.[67]

Stará and Starý used triflates and nonaflates for the conversion of 3-hexahelicenol to the C, N, P and S analogues.[68] Reaction of a 3-hexahelicenol-based nonaflate under a CO atmosphere and with palladium catalysis [$Pd(OAc)_2$/dppe] in DMSO/MeOH afforded the methoxycarbonylated product in 89% yield, whereas the corresponding triflate provided only 59%, again showing the superior behaviour of the aryl nonaflate.

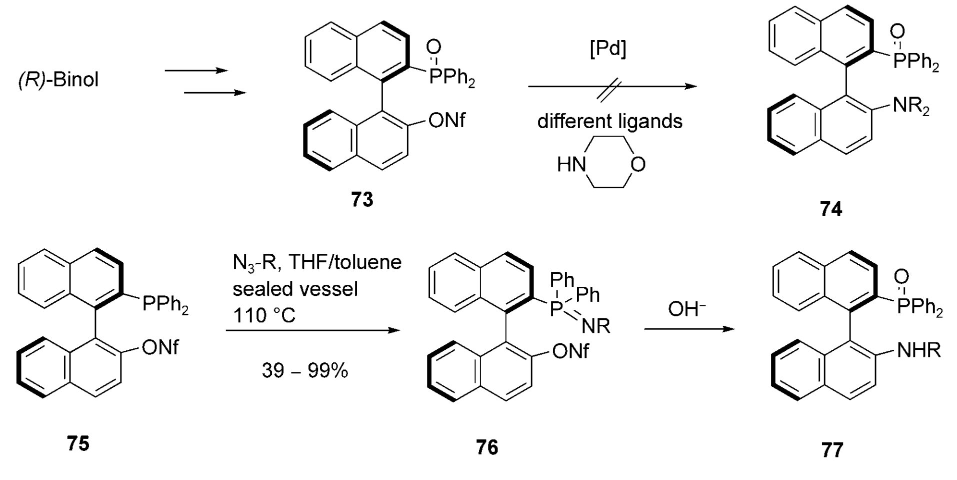
Aryl nonaflates and aryl triflates can be reduced in the presence of palladium to provide the corresponding arenes. Subramanian and Martinez used palladium on charcoal and hydrogen for this transformation reducing several aryl nonaflates in excellent yields.[69] A similar example was disclosed by Horwitz et al. who successfully applied H_2/Pd to the reduction of an aryl nonaflate during the synthesis of an estratrienol derivative.[70] An interesting alternative method was developed by Lipshutz et al. They employed dimethylamine borane complexes under palladium catalysis for the reduction of several aryl nonaflates. The products were obtained in very good yields.[71]



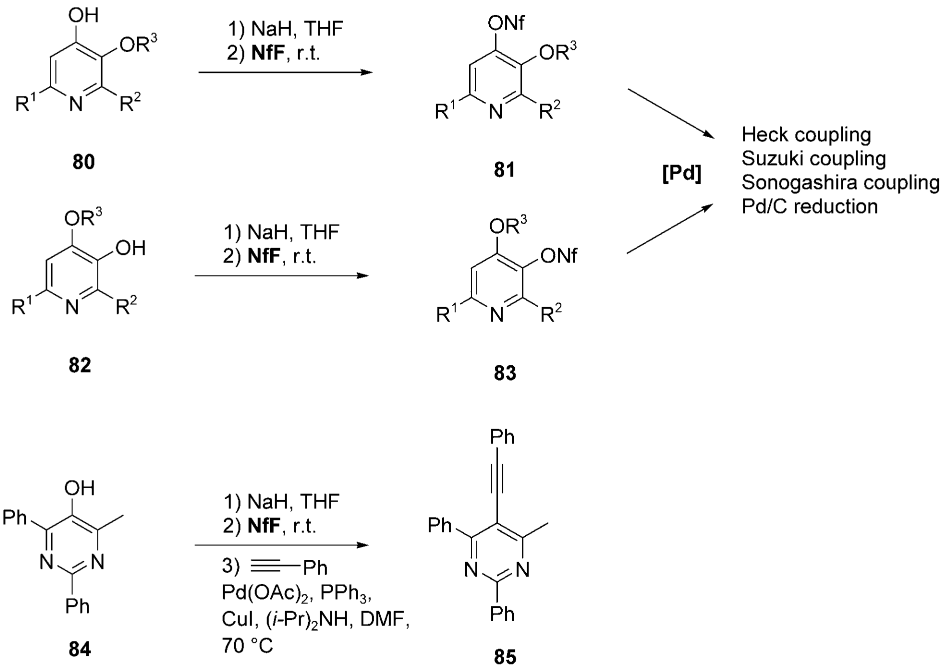
Scheme 25. Synthesis of BH_3-stabilized triarylphosphines **79**.

So far only a limited number of hetaryl nonaflates has been used in synthetic transformations. Our group prepared highly substituted pyridyl nonaflates that were successfully used for different palladium-catalyzed coupling reactions such as Heck, Suzuki and Sonogashira reactions as well as reductions with H_2/Pd/C.[72] Starting from 4-pyridinol derivatives such as **80** NaH/**NfF** furnished 4-pyridyl nonaflates **81** (Scheme 26). The regioisomeric 3-pyridinol derivatives **82** were similarly converted into 3-pyridyl nonaflates **83** and subjected to coupling reactions.[72d]

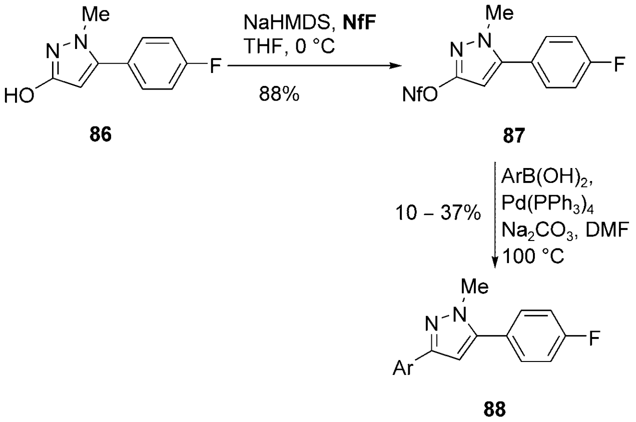
A pyrimidinyl nonaflate was prepared under standard conditions from compound **84** and a Sonogashira reaction with phenylacetylene provided the coupling product **85** in good yield.[73] Quinoline-derived nonaflates were used in Heck reactions with homoallyl alcohols which provided products required for SmI_2-induced syntheses of new azasteroid analogues.[74] Collins et al. prepared 1-methyl-3,5-diarylpyrazoles *via* Suzuki reactions.[75] The nonaflate **87** was synthesized using the combination NaHMDS/**NfF** and then coupled to products **88** in moderate to good yields (Scheme 27).



Scheme 24. Staudinger approach for the synthesis of binaphthyl-based P,N ligands **77**.



Scheme 26. Synthesis of 4- and 3-pyridyl nonaflates **81** and **83** as versatile precursors for coupling reactions and conversion of 4-pyrimidinol **84** into disubstituted alkyne derivative **85**.



Scheme 27. Preparation of diarylpyrazoles **88** *via* palladium-catalyzed couplings of pyrazolyl nonaflates.

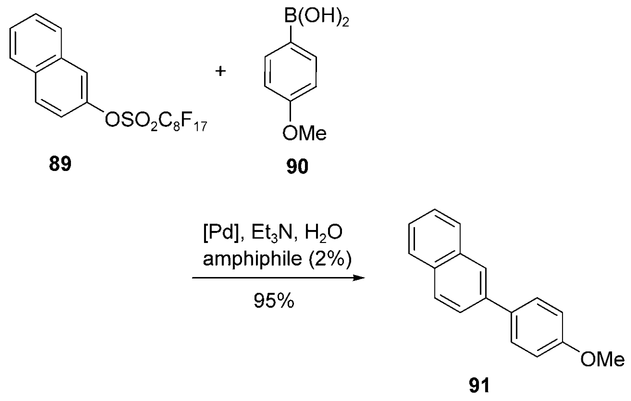
An example of a C–N coupling of a hetaryl sulfonate was reported by Cacchi et al. who aminated 2-pyridyl nonaflate with morpholine in 52% yield.[76]

5 Miscellaneous Reactions Including other Perfluorosulfonylated Reagents or Intermediates

Nonafluorobutanesulfonates have been used in a variety of other reactions that do not fit into the above categories. Therefore all these miscellaneous reactions are briefly summarized in this section. A new approach to highly functionalized azo compounds utilizing nonafluorobutanesulfonylbenzotriazoles (BtNf) has been reported by Subramanian and Ziegler.[77] BtNf can easily be prepared from lithiated benzotriazole and **NfF** in 89% yield. Treatment of phenols with this reagent led to *ortho*-substituted azobenzenes in good yields. Similarly, BtNf reacts with active methylene compounds such as diethyl malonates to furnish α-functionalized arylhydrazones. Wakselman et al. prepared aliphatic fluorinated sulfoximines by treatment of sulfoximines with NaH/**NfF**.[78]

The higher homologues of nonaflates, for example, C_8F_{17}-sulfonates, have also been used in Suzuki couplings. The group of Zhang demonstrated that these longer chain aryl perfluoroalkanesulfonates behave like aryl nonaflates providing the desired products in good yields.[79] Aryl perfluorooctanesulfonates were successfully employed in Buchwald–Hartig-type aminations.[80] This perfluoroalkanesulfonate reagent was explored by Lipshutz et al. for room temperature Suzuki couplings in water which is facilitated by non-ionic amphiphiles. This group found that the $C_8F_{17}SO_3$ derivatives displayed a considerably better reactivity than the corresponding triflates.[81] Compound **89** was coupled with boronic acid **90** under aqueous conditions giving **91** in 95% yield (Scheme 28). The corresponding triflate provided **91** with inferior efficacy. The lower homologues of nonaflates, tetraflates ($C_2F_4HSO_2$-OR) were also applied to Suzuki and Heck couplings as well as Pd-catalyzed amination reactions.[82]

Recently examples of solid phase-supported chemistry involving perfluoroalkanesulfonates have



Scheme 28. 2-Naphthyl perfluorooctanesulfonate **89** as precursor in a palladium-catalyzed reaction.

been reported. The group of Holmes developed a perfluoroalkanesulfonyl linker for the deoxygenation of phenols.[83a] This reactive R-$(CF_2)_2O(CF_2)_2SO_2F$ moiety **92** is linked *via* the R group to a resin and it was reacted with phenols using K_2CO_3 as base providing perfluoroalkanesulfonates **93** attached to the solid support (Scheme 29). Subsequent treatment with formic acid as hydrogen source in the presence of palladium furnished the deoxygenated products **94**, whereas the perfluoroalkyl moiety was removed traceless by filtering off the resin. In the same fashion this group also demonstrated that they were able to perform Suzuki reactions. The perfluoroalkanesulfonates **93** were coupled with boronic acids to furnish biaryls **95** in good yields.

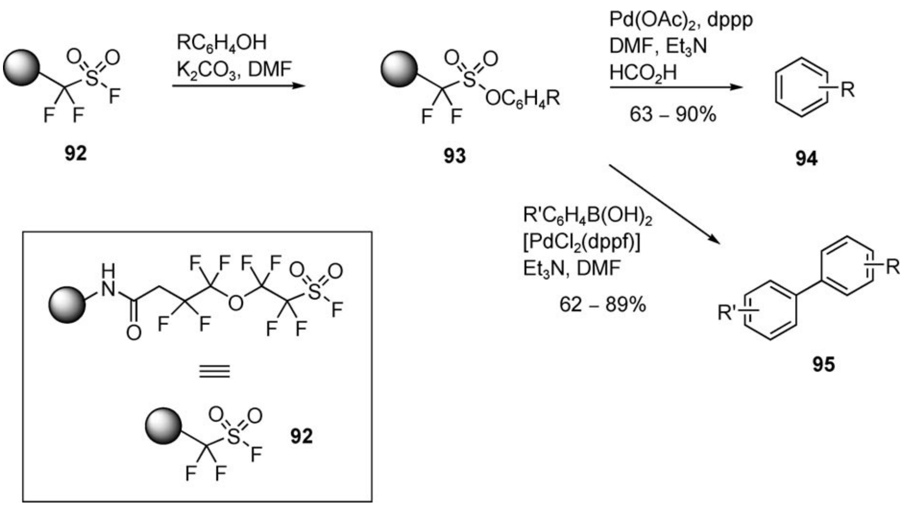
Another solid phase-supported reaction of an aryl nonaflate was disclosed by König.[84] A PEG 6000-connected phenol linked *via* an ester moiety to the solid phase support was converted into the corresponding nonaflate with triethylamine/**NfF**. This aryl nonaflate was then subjected to Suzuki reactions with arylboronic acids to afford the desired products in good yields. This report reveals that couplings on solid phase support with aryl nonaflates can easily be carried out.

A solid phase supported synthesis of ^{18}F-labelled 2-fluoro-2-deoxy-D-glucose using a perfluorinated linker [-$(CF_2)_2O(CF_2)_2SO_3$-] was reported by Brown and coworkers.[85] They developed an efficient protocol that involved the synthesis of a solid support-bound glucose derivative which was then treated with K^{18}F in the presence of kryptofix[2.2.2] in CH_3CN to give the fluorinated carbohydrate derivative in very short time with an ^{18}F incorporation of 70–91%. The carbohydrate moiety is elegantly cleaved by nucleophilic displacement of the linker sulfonate with K^{18}F during the reaction. The radio-labelled compound can be obtained without effort as the perfluorinated reagent is still connected to the resin.

1,3-Dipolar cycloadditions of nonaflyl azides were investigated by Zhu et al. Reactions of NfN_3 and 1,2-dihydropyridines did not give the expected cycloadducts but rather tetrahydropyridylidene fluoroalkanesulfonylamides.[86a] Similarly, cyclic vinyl ethers gave tetrahydropyran- and tetrahydrofuran-2-imines.[86b] In the case of simple vinyl ethers the primary triazolines could be isolated.[86c] Yamamoto used Nf-protected amines for the asymmetric hydroamination of alkynes. The linear alkynylamines were cyclized using chiral palladium complexes.[87]

Besides **NfF** recently an alternative nonaflyl transfer reagent has been reported: the group of Zhu found that (like 4-nitrophenyl triflate) 4-nitrophenyl nonaflate acts as potent perfluoroalkanesulfonyl transfer agent, providing a number of aryl nonaflates in good to excellent yields.[88] This group included theoretical calculations on the mechanism of the sulfonylation reaction.

An application employing a fluorous separation technique was reported by Wang et al.[89] who synthe-



Scheme 29. Solid supported palladium-catalyzed reactions with R-$(CF_2)_2O(CF_2)_2SO_3$-linked aryl groups.

sized (*S*)-pyrrolidine-sulfonamides tagged with CF_3, C_4F_9 and C_8F_{17} moieties. The pyrrolidines were used in organocatalytic enantioselective Michael additions of ketones and aldehydes to nitroolefins[89a] and for aldol reactions[89b] in water. All fluorous tagged catalysts gave good *ee*s and excellent yields. The C_4F_9-tagged sulfonamide was separated using fluorous silica gel separation techniques and recovered by washing the flash gel subsequently. The catalyst was reused for six subsequent cycles showing that nonafluorobutanesulfonyl-derived compounds can nicely be employed with fluorous separation techniques.[90] An *N*-nonafluorobutanesulfonylproline-Rh(II) complex was used by Corey et al. for the enantioselective insertion of carbenoids into silicon-hydrogen bonds efficiently leading to silylated cyclohexenones and cyclopentenones.[91]

6 Conclusion

Triflates are still the commonly employed reactive intermediates for most of the synthetically important coupling reactions starting from carbonyl compounds or aryl systems derived from phenols and their (hetero)analogues. This may be a matter of convenience since triflating reagents are readily available in a synthetic laboratory and several compounds can be purchased. Teaching habits may also support this. The many examples presented in this review witness that alkenyl, aryl, or heteroaryl nonaflates display remarkable advantages and are often clearly superior to triflates: 1) nonaflates are more stable, for example, to hydrolysis, and thus they can be purified by chromatography or other methods and stored for longer periods without decomposition; 2) in spite of this higher stability nonaflates are slightly more reactive[92] in most of the coupling reactions employed; 3) nonaflates are less prone to side reactions such as $O-SO_2$ bond cleavage processes.

All these advantageous properties generally lead to higher yields for the nonaflation and the coupling steps. The most commonly employed nonaflation reagent **NfF** is commercially available for a fair prize also in a large scale. If its moderate reactivity is not sufficient in the nonaflation step or if the released counter-ion fluoride is not desired, the corresponding anhydride (NfONf) can be purchased. For higher selectivity in the nonaflation alternatives such as the above mentioned 4-nitrophenyl nonaflate are already known or they should be easily available (e.g., the analogue of Comins reagents).[93] Not surprisingly, there are currently many attempts to substitute perfluorinated sulfonates in metal-catalyzed reactions by more cost effective alternatives such as tosylates,[94] mesylates[95] or imidazolylsulfonates.[96] Nevertheless, we are convinced that nonaflates (or their higher homologues) will be employed more frequently in laboratory or industrial scale once researchers have fully recognized the remarkable superiority of these perfluoroalkanesulfonates in metal promoted transformations.[97]

7 Supplement Added in Proof

Two palladium-catalyzed processes under formation of C–C and C–N bonds involving aryl nonaflates have been reported. The modular indole synthesis of Barluenga, Valdés et al. starts from imines and *o*-chlorononaflates.[98] A conversion of aryl nonaflates into nitroaromatic compounds was recently described by Fors and Buchwald.[99]

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References

[1] P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85–126.

[2] a) K. Ritter, *Synthesis* **1993**, 735–762; b) I. Baraznenok, V. Nenajdenko, E. Balenkova, *Tetrahedron* **2000**, *56*, 3077–3119; c) Z. Gilson, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680.

[3] a) H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägerloh, T. Oesterle, W. Steppan, W. West, G. Simchen, *Synthesis* **1982**, 1–26; b) H. Vorbrüggen, *Silicon-Mediated Transformation of Functional Groups*, Wiley-VCH, Weinheim, **2004**.

[4] R. Zimmer, M. Webel, H.-U. Reissig, *J. prakt. Chem.* **1998**, *340*, 274–277.

[5] V. Beyl, H. Niederprüm, P. Voss, *Liebigs Ann. Chem.* **1970**, *731*, 58–66.

[6] H. Vorbrüggen, *Synthesis* **2008**, 1165–1174.

[7] B. Bennua-Skalmowski, K. Kroliekiewcz, H. Vorbrüggen, *Bull. Soc. Chim. Belg.* **1994**, *103*, 453–461.

[8] B. Bennua-Skalmowski, H. Vorbrüggen, *Tetrahedron Lett.* **1995**, *36*, 2611–2614.

[9] R. A. Decréau, C. M. Marson, *Synth. Commun.* **2004**, *34*, 4369–4385.

[10] D. Zhou, K. E. Carlson, J. A. Katzenellenbogen, M. J. Welch, *J. Med. Chem.* **2006**, *49*, 4737–4744.

[11] B. Bennua-Skalmowski, H. Vorbrüggen, *Nucleosides Nucleotides* **1996**, *15*, 739–742.

[12] a) K. Izawa, S. Takamatsu, S. Katayama, N. Hirose, S. Kozai, T. Marauyama, *Nucleosides Nucleotides* **2003**, *22*, 507–517; b) T. Torii, T. Onishi, K. Izawa, T. Maruyama, *Tetrahedron Lett.* **2006**, *47*, 6139–6141; c) S. Ta-

kamatsu, S. Katayama, N. Hirose, E. De Cock, G. Schelkens, M. Demillequand, J. Breboels, K. Izawa, *Nucleosides Nucleotides* **2002**, *21*, 849–861.
[13] J. Yin, D. S. Zarkowsky, D. W. Thomas, M. M. Zhao, M. A. Huffman, *Org. Lett.* **2004**, *6*, 1465–1468.
[14] U. Klar, G. Neef, H. Vorbrüggen, *Tetrahedron Lett.* **1996**, *37*, 7497–7498.
[15] J. E. G. Kemp, M. D. Closier, S. Narayanaswami, M. H. Stefaniak, *Tetrahedron Lett.* **1980**, *21*, 2991–2994.
[16] a) E. Hirsch, S. Hünig, H.-U. Reissig, *Chem. Ber.* **1982**, *115*, 3687–3696; b) U. Hertenstein, S. Hünig, H. Reichelt, R. Schaller, *Chem. Ber.* **1986**, *119*, 699–721.
[17] M. Webel, H.-U. Reissig, *Synlett* **1997**, 1141–1142.
[18] a) I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2001**, 4189–4194; b) I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2002**, 1015–1025.
[19] M. A. K. Vogel, C. B. W. Stark, I. M. Lyapkalo, *Synlett* **2007**, 2907–2911.
[20] I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Synlett* **2001**, 1293–1295.
[21] I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2002**, 3646–3658.
[22] M. A. K. Vogel, C. B. W. Stark, I. M. Lyapkalo, *Adv. Synth. Catal.* **2007**, *349*, 1019–1024.
[23] I. M. Lyapkalo, J. Högermeier, H.-U. Reissig, *Tetrahedron* **2004**, *60*, 7721–7729.
[24] J. Högermeier, H.-U. Reissig, I. Brüdgam, H. Hartl, *Adv. Synth. Catal.* **2004**, *346*, 1868–1879.
[25] J. Högermeier, H.-U. Reissig, *Chem. Eur. J.* **2007**, *13*, 2410–2420.
[26] J. Högermeier, H.-U. Reissig, *Tetrahedron* **2007**, *63*, 8485–8491.
[27] a) J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006; b) J. Takagi, A. Kamon, T. Ishiyama, N. Miyaura, *Synlett* **2002**, 1880–1882.
[28] J. Högermeier, H.-U. Reissig, *Synlett* **2006**, 2759–2762.
[29] a) I. M. Lyapkalo, M. A. K. Vogel, *Angew. Chem.* **2006**, *118*, 4124–4127; *Angew. Chem. Int. Ed.* **2006**, *45*, 4019–4023; b) for the conversion of carbonyl compounds into alkynes see: I. M. Lyapkalo, M. A. K. Vogel, E. V. Boltukhina, *Synlett* **2009**, 558–561.
[30] S. Bräse, A. de Meijere, *Angew. Chem.* **1995**, *107*, 2741–2743; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2545–2547.
[31] K. Voigt, P. von Zezschwitz, K. Rosauer, A. Lansky, A. Adams, O. Reiser, A. de Meijere, *Eur. J. Org. Chem.* **1998**, 1521–1534.
[32] A. Wada, Y. Ieki, M. Ito, *Synlett* **2002**, 1061–1064.
[33] A. Wada, Y. Ieki, S. Nakamura, M. Ito, *Synthesis* **2005**, 1581–1588.
[34] J. Suffert, A. Eggers, S. W. Scheuplein, R. Brückner, *Tetrahedron Lett.* **1993**, *34*, 4177–4180.
[35] W. D. Shipe, E. J. Sorensen, *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035.
[36] F. Bellina, D. Ciucci, R. Rossi, P. Vergatini, *Tetrahedron* **1999**, *55*, 2103–2122.
[37] a) R. K. Dieter, G. Oba, K. R. Chandupatla, C. M. Topping, K. Lu, R. T. Watson, *J. Org. Chem.* **2004**, *69*, 3076–3086; b) S. Li, R. K. Dieter, *J. Org. Chem.* **2003**, *68*, 969–973.
[38] G. Dunet, P. Knochel, *Synlett* **2006**, 407–410.
[39] S. Bräse, *Synlett* **1999**, 1654–1656.
[40] T. Okauchi, T. Yano, T. Fukamachi, J. Ichikawa, T. Minami, *Tetrahedron Lett.* **1999**, *40*, 5337–5340.
[41] S. Inoue, T. Okauchi, T. Minami, *Synthesis* **2003**, 1971–1976.
[42] X. Han, B. M. Stoltz, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
[43] B. M. Stoltz, T. Kano, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9044–9045.
[44] a) W. P. Gallagher, R. E. Maleczka Jr., *Synlett* **2003**, 537–541; b) W. P. Gallagher, R. E. Maleczka Jr., *J. Org. Chem.* **2003**, *68*, 6775–6779.
[45] Z. Zhu, T. M. Swager, *Org. Lett.* **2001**, *3*, 3471–3474.
[46] M. Uemura, H. Yorimitsu, K. Oshima, *Tetrahedron* **2008**, *64*, 1829–1833.
[47] M. Rottländer, P. Knochel, *J. Org. Chem.* **1998**, *63*, 203–208.
[48] A. E. Jensen, W. Dohle, P. Knochel, *Tetrahedron* **2000**, *56*, 4197–4201.
[49] a) A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Org. Lett.* **2005**, *7*, 4871–4874; b) A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Tetrahedron* **2006**, *62*, 7521–7533.
[50] a) M. Biagetti, F. Bellina, A. Carpita, P. Stabile, R. Rossi, *Tetrahedron* **2002**, *58*, 5023–5038; b) R. Rossi, A. Carpita, F. Bellina, P. Stabile, L. Mannina, *Tetrahedron* **2003**, *59*, 2067–2081.
[51] S. E. Denmark, R. F. Sweis, *Org. Lett.* **2002**, *4*, 3771–3774.
[52] S. Hillers, O. Reiser, *Tetrahedron Lett.* **1993**, *34*, 5265–5268.
[53] J. C. Namyslo, D. E. Kaufmann, *Chem. Ber.* **1997**, *130*, 1327–1331.
[54] X. Zhang, Z. Sui, *Tetrahedron Lett.* **2003**, *44*, 3071–3073.
[55] K. W. Anderson, M. Mendez-Perez, J. Priego, S. L. Buchwald, *J. Org. Chem.* **2003**, *68*, 9563–9573.
[56] R. E. Tundel, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2006**, *71*, 430–433.
[57] See also: R. E. Meadows, S. Woodward, *Tetrahedron* **2008**, *64*, 1218–1224.
[58] B. H. Lipshutz, D. J. Buzard, C. Olsson, K. Noson, *Tetrahedron* **2004**, *60*, 4443–4449.
[59] C. Bolm, J. P. Hildebrand, J. Rudolph, *Synthesis* **2000**, 911–913.
[60] D. Le Goanvic, M. A. Tius, *J. Org. Chem.* **2006**, *71*, 7800–7804.
[61] P. N. M. Botman, J. Fraanje, K. Goubitz, R. Peschar, J. W. Verhoeven, J. H. van Maarseveen, H. Hiemstra, *Adv. Synth. Catal.* **2004**, *346*, 743–754.
[62] P. N. M. Botman, O. David, A. Amore, J. Dinkelaar, M. T. Vlaar, K. Goubitz, J. Fraanje, H. Schenk, H. Hiemstra, J. H. van Maarseveen, *Angew. Chem.* **2004**, *116*, 3553–3555; *Angew. Chem. Int. Ed.* **2004**, *43*, 3471–3473.
[63] a) F. Y. Kwong, K. S. Chan, *Organometallics* **2001**, *20*, 2570–2578; b) Y. Wang, C. W. Lai, Y. Fuk, W. Jia, K. S. Chan, *Tetrahedron* **2004**, *60*, 9433–9439.
[64] a) F. Y. Kwong, C. W. Lai, K. S. Chan, *J. Am. Chem. Soc.* **2001**, *123*, 8864–8865; b) F. Y. Kwong. C. W. Lai, M. Yu, D. M. Tan, F. L. Lam, A. S. C. Chan, K. S. Chan, *Organometallics* **2005**, *24*, 4170–4178.

[65] M. Al-Masum, T. Livinghouse, *Tetrahedron Lett.* **1999**, *40*, 7731–7734.

[66] B. H. Lipshutz, D. J. Buzard, C. S. Yun, *Tetrahedron Lett.* **1999**, *40*, 201–204.

[67] M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, *65*, 164–168.

[68] F. Teply, I. G. Stará, I. Starý, A. Kollárovic, D. Saman, S. Vyskocil, P. Fiedler, *J. Org. Chem.* **2003**, *68*, 5193–5197.

[69] L. R. Subramanian, A. Garcia Martinez, A. Herrera Fernandez, R. Martinez Alvarez, *Synthesis* **1984**, 481–485.

[70] J. P. Horwitz, V. K. Iyer, H. B. Vardhan, J. Corombos, S. C. Brooks, *J. Med. Chem.* **1986**, *29*, 692–698.

[71] a) B. H. Lipshutz, D. J. Buzard, R. W. Vivian, *Tetrahedron Lett.* **1999**, *40*, 6971–6974; b) B. H. Lipshutz, B. A. Freiman, T. Butler, V. Kogan, *Angew. Chem.* **2006**, *118*, 814–817; *Angew. Chem. Int. Ed.* **2006**, *45*, 800–803; c) for a recent application see: C. J. Rohbogner, G. C. Clososki, P. Knochel, *Angew. Chem.* **2008**, *120*, 1526–1530; *Angew. Chem. Int. Ed.* **2008**, *47*, 1503–1507.

[72] a) O. Flögel, J. Dash, I. Brüdgam, H. Hartl, H.-U. Reissig, *Chem. Eur. J.* **2004**, *10*, 4283–4290; b) J. Dash, T. Lechel, H.-U. Reissig, *Org. Lett.* **2007**, *9*, 5541–5544; c) J. Dash, H.-U. Reissig, *Chem. Eur. J.* **2009**, *15*, 6811–6814; d) T. Lechel, J. Dash, I. Brüdgam, H.-U. Reissig, *Eur. J. Org. Chem.* **2008**, 3647–3655.

[73] T. Lechel, S. Möhl, H.-U. Reissig, *Synlett* **2009**, 1059–1062.

[74] a) F. Aulenta, H.-U. Reissig, *Synlett* **2006**, 2993–2996; b) F. Aulenta, U. K. Wefelscheid, I. Brüdgam, H.-U. Reissig, *Eur. J. Org. Chem.* **2008**, 2325–2335.

[75] S. Bourrain, M. Ridgill, I. Collins, *Synlett* **2004**, 795–798.

[76] S. Cacchi, A. Carangio, G. Fabrizi, L. Moro, P. Pace, *Synlett* **1997**, 1400–1402.

[77] a) X. W. Micó, T. Ziegler, L. R. Subramanian, *Angew. Chem.* **2004**, *116*, 1424–1427; *Angew. Chem. Int. Ed.* **2004**, *43*, 1400–1403; b) M. U. Anwar, S. Tragl, T. Ziegler, L. R. Subramanian, *Synlett* **2006**, 627–629; c) M. Uhde, T. Ziegler, *Synthesis* **2009**, 1190–1194.

[78] E. Magnier, C. Wakselman, *Synthesis* **2003**, 565–569.

[79] W. Zhang, C. Hiu-Tung Chen, Y. Lu, T. Nagashima, *Org. Lett.* **2004**, *6*, 1473–1476.

[80] W. Zhang, T. Nagashima, *J. Fluorine Chem.* **2006**, *127*, 588–591.

[81] B. H. Lipshutz, T. B. Petersen, A. R. Abela, *Org. Lett.* **2008**, *10*, 1333–1336.

[82] V. V. Rostovtsev, L. M. Bryman, C. P. Junk, M. A. Harmer, L. G. Carcani, *J. Org. Chem.* **2008**, *73*, 711–714.

[83] a) Y. Pan, C. P. Holmes, *Org. Lett.* **2001**, *3*, 2769–2771; b) Y. Pan, B. Ruhland, C. P. Holmes, *Angew. Chem.* **2001**, *113*, 4620–4623; *Angew. Chem. Int. Ed.* **2001**, *40,* 4488–4491.

[84] C. G. Blettner, W. A. König, W. Stenzel, T. Schotten, *J. Org. Chem.* **1999**, *64*, 3885–3890.

[85] L. J. Brown, D. R. Bouvet, S. Champion, A. M. Gibson, Y. Hu, A. Jackson, I. Khan, N. Ma, N. Millot, H. Wadsworth, R. C. D. Brown, *Angew. Chem.* **2007**, *119*, 959–962; *Angew. Chem. Int. Ed.* **2007**, *46*, 941–944.

[86] a) Y. Xu, Y. Wang, S. Zhu, G. Zhu, Y. Jia, Q. Huang, *J. Fluorine Chem.* **2000**, *106*, 133–138; b) S.-Z. Zhu, G.-F. Jin, J.-W. Zhao, *J. Fluorine Chem.* **2003**, *120*, 65–69; c) S.-Z. Zhu, P. He, J.-W. Zhao, X. Cai, *J. Fluorine Chem.* **2004**, *125*, 445–450.

[87] a) L. M. Lutete, I. Kadota, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623; b) G. B. Bajracharya, Z. Huo, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4883–4886; c) N. T. Patil, L. M. Lutete, H. Wu, N. K. Phahadi, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2006**, *71*, 4270–4279; d) M. Narsireddy, Y. Yamamoto, *J. Org. Chem.* **2008**, *73*, 9698–9709.

[88] L. Neuville, A. Bigot, M. E. T. Huu Dau, J. Zhu, *J. Org. Chem.* **1999**, *64*, 7638–7642.

[89] a) L. Zu, J. Whang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079; b) L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Org. Lett.* **2008**, *10*, 1211–1214.

[90] A definition for fluorous separation technique has been introduced: "a fluorous separation technique is any method that separates fluorous or fluorous-labelled molecules from other types of molecules, or from each other, based primarily on the structure of the fluorous domain of the molecules." I. T. Horváth, D. P. Curran, J. A Gladysz, in: *Handbook of Fluorous Chemistry*, Wiley-VCH, Weinheim, **2004**. In general, the nonaflate derivatives described in this review do not cause a clear fluorous effect. For an exception, see ref.[89]

[91] M. Ge, E. J. Corey, *Tetrahedron Lett.* **2006**, *47*, 2319–2321.

[92] We found that nonaflates are more reactive than the corresponding triflates in several palladium-catalyzed transformations, however, the ratio strongly depends on the reaction, ranging from 1.1 to 1.9 in favour of the nonaflate. J. Högermeier, *Dissertation*, Freie Universität Berlin, **2006**; M. Taszarek, *Diplomarbeit*, Freie Universität Berlin, **2007**. Also see ref.[47] stating higher reactivity of nonaflates.

[93] a) D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299–6302; b) D. L. Comins, A. Dehghani, C. J. Foti, S. P. Joseph, *Org. Synth. 74*, 77; *Org. Synth.* Coll. Vol. IX, 74; c) J. E. McMurry, W. J. Scott, *Tetrahedron Lett.* **1983**, *24*, 979–982.

[94] For some recent examples employing tosylates, see: A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby, T. Skrydstrup, *Angew. Chem.* **2006**, *118*, 3427–3431; *Angew. Chem. Int. Ed.* **2006**, *45*, 3349–3353. L. Ackermann, A. Althammer, *Org. Lett.* **2006**, *8*, 3457–3460. H. Nakatsuji, K. Ueno, T. Misaki, Y. Tanabe, *Org. Lett.* **2008**, *10*, 2131–2134. B. Bhayana, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 3954–3957.

[95] For some recent examples employing mesylates, see: C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 8179–8183; *Angew. Chem. Int. Ed.* **2008**, *47*, 8059–8063. L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem.* **2009**, *121*, 207–210; *Angew. Chem. Int. Ed.* **2009**, *48*, 201–204. J.-i. Kuroda, K. Inamoto, K. Hiroya, T. Doi, *Eur. J. Org. Chem.* **2009**, 2251–2261.

[96] For the use of imidazolylsulfonates, see: J. Albaneze-Walker, R. Raju, J. A. Vance, A. J. Goodman, M. R. Reeder, J. Liao, M. T. Maust, P. A. Irish, P. Espino, D. R. Andrews, *Org. Lett.* **2009**, *11*, 1463–1466.

[97] For selected recent reviews, see: J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2652–2710; A. Roglans, A. Pla-Quintana, M. Moreno-Manas, *Chem. Rev.* **2006**, *106*, 4622–4643; Y. Lin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133–173; R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874–922; D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; A. Brennführer, H. Neumann, M. Beller, *Angew. Chem.* **2009**, *121*, 4176–4196; *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133.

[98] J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.* **2009**, *131*, 4031-4041.

[99] B. P. Fors, S. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 12898-12899.