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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3841–3845

One-pot synthesis of α,α-difluoroimines from alkynes through tandem catalytic diboration/fluorination/imination reaction

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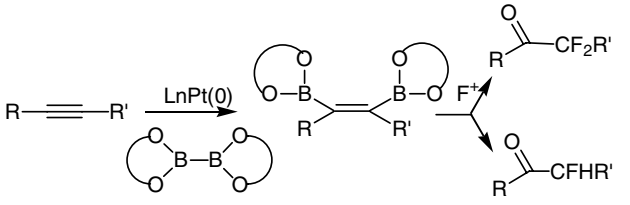
Received 19 February 2007; revised 26 March 2007; accepted 28 March 2007
Available online 3 April 2007

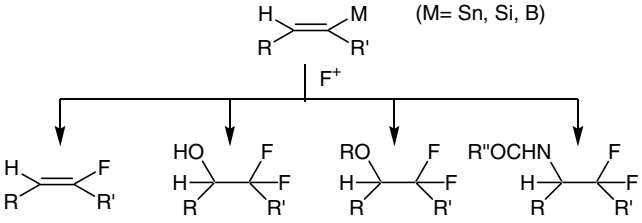
Abstract—Tandem catalytic diboration/fluorination/imination of arylacetylenes leads to the formation of α,α-difluoroimines, where the adjacent C=N and C–F_2 bonds are formed simultaneously. The convenient one-pot protocol involves a Pt(0)-catalyzed diboration of terminal or internal arylalkynes followed by electrophilic fluorination with Selectfluor in the presence of primary amines and a dehydrating agent. A plausible mechanism for the three consecutive steps (diboration/fluorination/imination) is suggested in accordance with the electronic properties of the substrates. Alkynes/catalytic diboration/alkenyl diboronate esters/Selectfluor/electrophilic fluorination/α,α-difluoroimines.

The selective transfer of a fluorine atom into an organic molecule has become a considerable challenge for chemists interested in biological and medicinal applications.[1] The formation of the C–F bond adjacent to the carbonyl or imine functionality increases the electrophilicity of these functional groups,[2] improving their bioactivity.[3] The direct synthesis of α-fluoroketones often involves the fluorofunctionalization of carbonyl-stabilized carbanions,[4] as in the electrophilic fluorination of metal enolates, silyl enol ethers, and enol acetates. On the other hand, fluorine ion displacement of a halide from α-halocarbonyl compounds, or the reaction of diazo derivatives with HF, have been shown to be alternative routes toward α-fluoroketones synthesis.[5] In this regard, we have recently described a more direct synthesis of α-fluoroketones and α,α-difluoroketones through a tandem catalytic diboration of alkynes followed by electrophilic fluorination protocol.[6] In that study, we determined the most favorable reaction conditions for selectively obtaining the α,α-difluoroketones versus α-fluoroketones with 2 equiv of easily-handled and cost-effective N–F reagents,[7] such as *Selectfluor*[8] (Scheme 1).

Our working hypothesis was based on the previous literature reports which demonstrated that an electrophilic fluorine source may react with alkenyl-metal compounds (M = Sn,[9] Si,[10] B[11]) to provide alkenyl fluorides and other structurally diverse compounds such as difluorinated amides, alcohols and ethers (Scheme 2).[9–11] Taking into account that the putative carbocationic intermediate can be quenched with water to produce difluoromethyl alcohol derivatives, we realized that an alkenyl diboronate ester could directly be functionalized toward the desired adjacent C=O and C–F bonds.



Scheme 1.



Scheme 2.

Keywords: Alkynes; Catalytic diboration; Alkenyl diboronate esters; Selectfluor; Electrophilic fluorination; α,α-Difluoroimines.
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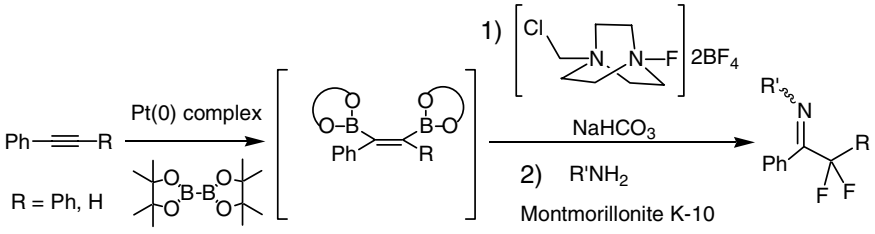
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.03.155

During our continuous study of the tandem diboration–functionalization reaction, we became interested in the direct fluorination toward the α,α-difluoroimines synthesis, as these compounds are considered interesting synthetic intermediates to fluorinated azaheterocyclic compounds and β-fluorinated amines.[12] To the best of our knowledge, two previous reports have described the direct electrophilic fluorination of imines.[13] More recently, a milder and efficient procedure for synthesizing and isolating either α-fluoroimines or α,α-difluoroimines via the direct electrophilic fluorination of ketimines using *N*-fluorobenzenesulfonimide (NFSI), has been reported.[14] However, all these attempts have the imine functionality as part of the substrate, and ketones derivatives from hydrolysis cannot be avoided. In this context we were aimed to explore an alternative synthetic method, in which the imine functionality could be formed simultaneously to the C–F formation. In this Letter, we report the first tandem approach for difluorofunctionalizing imines from alkynes substrates in a one-pot reaction.

In a typical experiment of the tandem catalytic diboration/fluorination/imination sequence involving conventional reflux heating (Scheme 3), phenylacetylene was first added to an acetonitrile solution that contained 3 mol % of Pt(0) catalytic precursor $Pt(PPh_3)_4$, (or alternatively Pt(NHC)[15] catalytic system), with an equimolar amount of the diborating reagent bis(pinacolato)diboron. After the mixture was stirred at reflux temperature (82 °C) for 15 h, 2 equiv of Selectfluor and 2.2 equiv of $NaHCO_3$ base were added to the crude preparation of *cis*-1,2-bis(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl) styrene. After an additional 15 h at room temperature, an NMR spectra of an aliquot showed the formation of the expected 2,2-difluoroacetophenone, with complete conversion of the substrate. The in situ addition of equimolecular amounts of $R'NH_2$ and Montmorillonite K-10 as dehydrating agent,[16] allowed the α,α-difluoroimine formation, after 15 h of reaction (Table 1). The products could be characterized by ^1H and ^{19}F NMR and GC–MS and the % yield was calculated using perfluoronaphthalene as an internal standard.

The direct formation of *gem*-difluorinated imines in this one-pot reaction protocol is particularly attractive, since it opens the perspective toward the in situ synthesis of the imine functionality when primary amine is present in the reaction media, thus avoiding any hydrolysis byproducts. The dehydrating capability of Montmorillonite K-10 (MK-10) was particularly shown for terminal α,α-difluoroimine formation (Table 1, entries 1–5). However, for internal α,α-difluoroimines, the use of MK-10 did not completely convert the α,α-difluoroketones into α,α-difluoroimine, even under refluxing conditions (Table 1, entries 6 and 7). Therefore, $TiCl_4$[17] was required to obtain a total imine transformation (Table 1, entries 8–10). The percentage of internal α,α-difluoroimine formation is superior to the terminal α,α-difluoroimines, which is in agreement with the fact that terminal alkenyldiboronates intermediates proved to be less reactive than internal alkenyldiboronates



Scheme 3.

Table 1. Tandem catalytic diboration/fluoriation/imination of alkynes[a,b]

Entry	Ar	R	Amine $R'NH_2$	Activating and dehydrating agent	α,α-Difluoroketone[c] (%)	α,α-Difluoroimine[c] (%)
1	C_6H_5	H	^{i}PrNH$_2$	MK-10	1	27
2	C_6H_5	H	^{n}BuNH$_2$	MK-10	—	33
3	*p*-(CF$_3$)-C$_6$H$_4$	H	^{n}BuNH$_2$	MK-10	—	26
4	*p*-(OMe)-C$_6$H$_4$	H	^{n}BuNH$_2$	MK-10	—	40
5	C_6H_5	H	CyNH$_2$	MK-10	—	19
6	C_6H_5	Ph	^{n}BuNH$_2$	MK-10	18	27
7	C_6H_5	Ph	^{n}BuNH$_2$	MK-10[d]	8	37
8	C_6H_5	Ph	^{n}BuNH$_2$	$TiCl_4$	—	45
9	C_6H_5	Ph	^{i}PrNH$_2$	$TiCl_4$	—	43
10	C_6H_5	Ph	CyNH$_2$	$TiCl_4$	—	42

[a] Standard conditions: *for catalytic diboration*: substrate/Pt catalyst ($Pt(PPh_3)_4$/diborane (bis(pinacolato)diboron) = 1/0.03/1; solvent: CH_3CN; *T*: 82 °C; *t*: 15 h. *For fluorination reaction*: Selectfluor/substrate/$NaHCO_3$ base = 2/1/2.2; solvent: CH_3CN; *T*: rt; *t*: 15 h. *For imination reaction*: $R'NH_2$/substrate = 1/1; activating and dehydrating reagents: Montmorillonite K-10 (MK-10) 100 mg or $TiCl_4$ 0.6 equiv; solvent: CH_3CN; *T*: 25 °C; *t*: 15 h.

[b] Quantitative conversion from the substrate.

[c] The reaction was monitored by ^1H NMR and ^{19}F NMR, in the presence of perfluoronaphthalene as an internal standard.

[d] Temperature for the imination step: 82 °C.

toward the electrophilic fluorination step.[6] Aliphatic terminal alkynes did not provide any fluorinated compounds, which is in agreement with the tendency observed by Olah et al.,[11] where the fluorination of alkenyl boronic acids and trifluoroboronates worked well only with compounds leading to benzylic carbocations.

In contrast to the efficiency of the *cis*-1,2-bis(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl) styrene derivatives, the corresponding *cis*-1,2-bis(1,3,2-benzodioxaborolan-2-yl) styrene was not fluorinated. A similar effect has previously been observed in the electrophilic fluorination of (*E*)-(2-phenylethenyl)catecholboronate and (*E*)-(2-phenylethenyl)trifluoroboronate.[11] The hexyleneglycolato alkenyl diboronate ester derivative, was also a suitable intermediate for the fluorination, with similar values to the pinacol derivative. This agrees with the fact that both the hexyleneglycolato and pinacolato alkenyl boronate esters, have previously been easily iodo- and chloro-deboronated in the past.[18]

Our current mechanistic understanding of this transformation suggests that the N–F reagents could react with alkenyl diboronate ester intermediates through an electrophilic attack. To confirm this, we investigated how far the electronic nature of the intermediate substituted alkenyl diboronate esters can affect the electrophilic fluorination process. The electronic properties of the substituents in the *para* position of phenylacetylene influence the electrophilic fluorination pathway. Apparently, the more electron rich the alkenyl diborated ester is, the more reactive toward the electrophilic fluorination it will be (Table 1, entries 2–4). This is in agreement with the indirect measurement of the chemical shift in the ^{1}H NMR of the alkenyldiboronate ester formed in situ during the catalytic diboration of the *para*-substituted phenylacetylenes. The ^{1}H NMR values for the alkenyl moiety increase from 6.21 ppm in *cis*-1,2-bis-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl) *p*-MeO-styrene to 6.34 ppm in *cis*-1,2-bis(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl) *p*-CF_3-styrene (Fig. 1). The differences in the chemical shift values could be due to the inductive effects of the *para*-substituents. In addition, the substituted alkenyl diboronate esters seem to react more efficiently than the corresponding substituted phenylacetylenes toward the electrophilic N–F fluorinating reagent, Selectfluor.

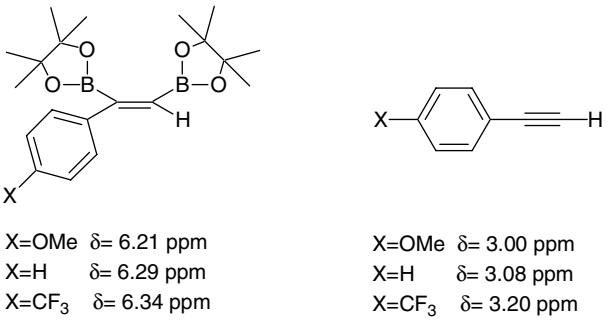
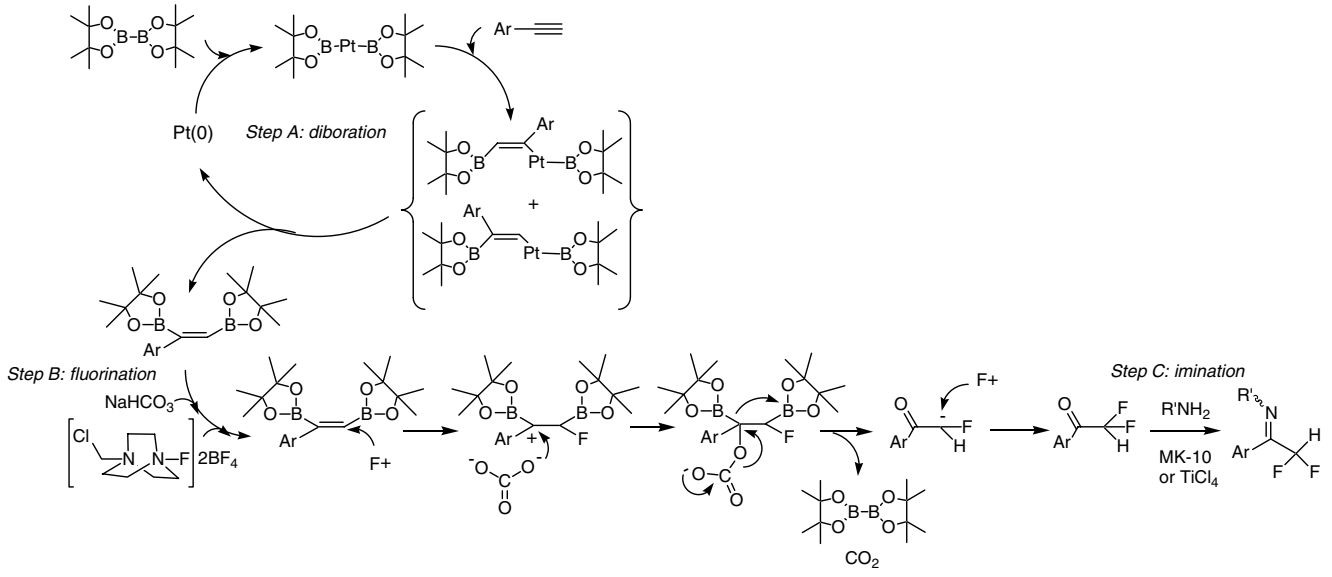


Figure 1.

The ^{1}H NMR is also consistent with the fact that the terminal vinyldiboranes are more nucleophilic than the aryl acetylenes (Fig. 1).

These results provide some insights into the mechanism of the fluorination process, especially when some authors had reported radical mechanisms in related fluorination processes.[19] A plausible mechanism for the overall tandem sequence is shown in Scheme 4. The catalytic cycle for the diboration of alkynes,[20] was first proposed by Miyaura et al.[21] through the oxidative addition of diboron to Pt(0), followed by the insertion of the alkyne into the Pt–B bond and finally the reductive elimination of the alkenyldiboronate esters to regenerate the Pt(0) catalytic system. Evidence for a Pt atom containing two cis boryl and phosphine ligands as an intermediate in the cycle has been generated by a single crystal structure.[22] The catalytic diboration reaction seems to



Scheme 4.

be significantly accelerated by unsaturated Pt(0) complexes having donating phosphine ligands[23] and to be slowed down in the presence of PPh_3 added to $Pt(PPh_3)_4$,[24,25] thus suggesting that both the oxidative addition and the phosphine dissociation have a rate-determining role.

Despite the fact that other Pt(0) derivatives such as $Pt(PPh_3)_2(C_2H_4)$,[24,26] mono(phosphine)platinum complexes,[23,25] Pt–N-heterocyclic carbene ligands[15] and base-free platinum[27] complexes have significantly improved the activity and selectivity of the diborated product, we selected $Pt(PPh_3)_4$ as a catalyst because of its commercial accessibility. As far as the fluorination step is concerned, we suggest a concerted mechanism in which the electrophilic attack of F^+ occurs at the most electronegative C–B bond in the alkenyldiboronate esters, followed by a nucleophilic attack of the carbonate base, ultimately leading to the formation of carbon dioxide and the regeneration of bis(pinacolato)diboron, with concomitant formation of the second C–F bond at the terminal position. However, deprotonation from the fluorinated cation by the carbonate to deliver a fluorinated olefin which could be eventually fluorinated again, can also be considered as an alternative pathway for the fluorination step. Two factors support this mechanism: (i) no fluorination is observed in the absence of base, and (ii) the formation of regenerated bis(pinacolato)diboron was confirmed by GC–MS analysis of the crude reaction mixture. A close oxidation protocol has recently been described to transform (fluoroalkenyl)boranes into α-fluoroketones.[28] Although we do not have evidences for the participation of a radical mechanism, we cannot discard it. Finally, the imination proceeds easily in the presence of the dehydrating agent.

In conclusion, although organoboron compounds are considered useful intermediates in organic synthesis, to the best of our knowledge, the only transformation of the two boryl units from the alkenyl diboronate ester, into interesting functional groups, has been described for the palladium-catalyzed C–C cross-coupling reaction with aryl, alkenyl, benzyl and allyl halides.[29] In this context, one of the most important issues we have addressed in this study is the conversion of two C–B bonds into the functionalized C=N and C–F bonds, thus providing a direct method that transforms arylacetylenes into α,α-difluoroimines. Experimentally we found that the efficiency of the tandem catalytic diboration/electrophilic fluorination/imination of aryl acetylenes depends on the electronic factors of the substrates. We expect this new synthetic approach to provide a convenient one-pot protocol to biological and medicinal α,α-difluoroimines from available terminal and internal aryl alkynes.

Acknowledgments

The authors thank the CTQ2004-04412/BQU for financial support and the Generalitat de Catalunya for providing J.R. with a fellowship, and 2005ACOM00026.

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