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NiH-Catalyzed Migratory Defluorinative Cross Olefin-Coupling: Trifluoromethyl-Substituted Alkenes as Acceptor Olefins to Form *gem*-Difluoroalkenes

Fenglin Chen, Xianfeng Xu, Yuli He, Genping Huang, and Shaolin Zhu*

Abstract: We report a nickel hydride-catalyzed migratory defluorinative coupling between two electronically-differentiated olefins. A broad scope of unactivated donor olefins can be joined directly to acceptor olefins containing an electron-deficient trifluoromethyl-substituent in both intra- and intermolecular fashions to form *gem*-difluoroalkenes. This migratory coupling has both site- and chemoselectivity under mild conditions, with the formation of a tertiary or quaternary carbon center.

gem-Difluoroalkenes are versatile precursors to a broad variety of organofluorine compounds which are widely used in agrochemicals, pharmaceuticals, and materials science.[1] Owing to their enhanced metabolic stability, such compounds are also ideal carbonyl bioisosteres useful in modern drug discovery due to their steric and electronic similarity to ketones, aldehydes, and esters (Figure 1a).[2] Consequently, considerable effort has been made towards their synthesis.[3] The *gem*-difluoromethylenation of carbonyl or diazo precursors is the direct approach for their construction,[4] but, as an alternative, catalytic defluorinative alkylation, sequential introduction of an alkyl group into the readily prepared CF_3-substituted alkene and β-fluorine-elimination, offers another promising approach.[5] This latter process usually requires the pregenerated organometallic reagents used in a metal-catalyzed S_N2'-type transformation or the prefunctionalized alkyl radical precursor used in a photocatalytic process. However, the requirement for pregenerated organometallic reagent or prefunctionalized alkyl radical precursor is less than ideal from the standpoints of step- and atom-economy, and the coupling is limited to the site of preinstalled reactive coupling groups.

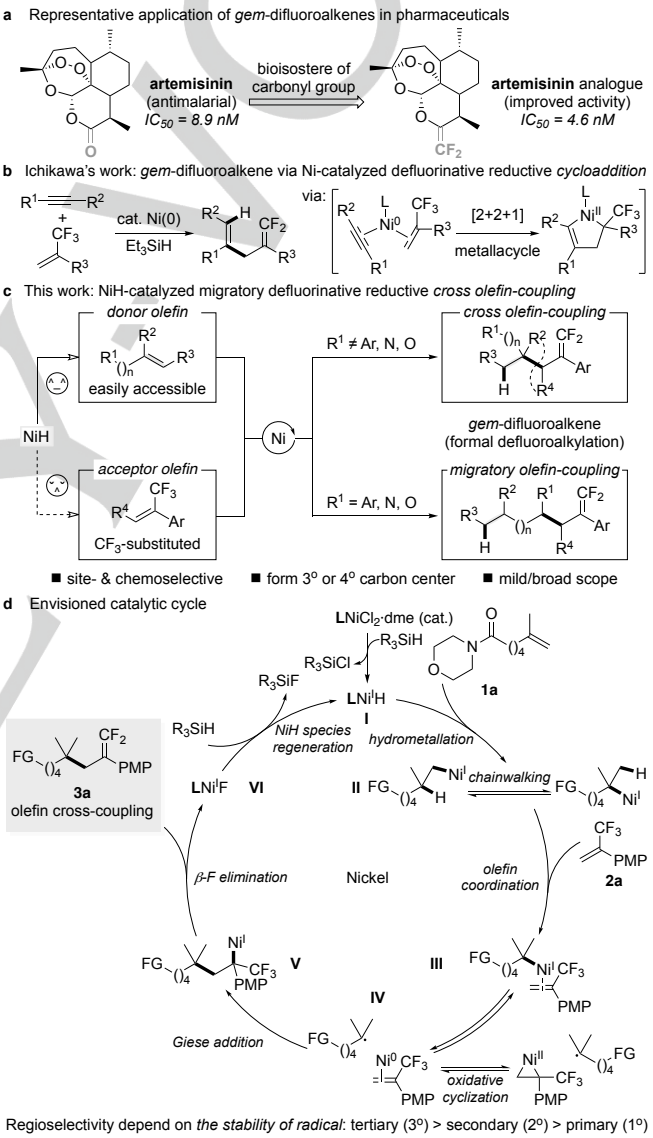

Figure 1. Site- and chemoselective (migratory) hydro-γ,γ-difluoroallylation of olefins.

Synergistic combination of chainwalking and cross-coupling, remote functionalization[6–10] has emerged as a general strategy with which to achieve inert sp^3 C–H bond functionalization not readily accessible *via* classical directing group pathways or harsh and potentially unselective non-directed C–H activation conditions. Recently, the abundant

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nickel-catalyzed remote functionalization of olefins has attracted considerable interest.[10] In this process, easily accessible and bench-stable unsaturated hydrocarbons are used as latent nucleophile equivalents, obviating the need for multistep prefunctionalization. Cross-couplings happen selectively at remote sp^3 C–H bonds with traditional coupling partners. Although the NiH-catalyzed migratory olefin polymerization is a well-known industrial process,[11] a site- and chemoselective catalytic system for the migratory coupling between a donor olefin and an acceptor olefin remains elusive.[12] Stimulated by Ichikawa's pioneering studies on Ni-catalyzed defluorinative reductive cycloaddition of trifluromethyl alkenes with alkynes (Figure 1b),[5f] we propose a NiH-catalyzed[13] migratory defluorinative coupling process between unactivated donor olefins and CF_3-substituted acceptor olefins to rapidly introduce a *gem*-difluoroalkene unit into targets (Figure 1c).

Our proposed mechanism is outlined in Figure 1d. A NiH species, generated *in situ*, would selectively initiate a rapid chainwalking process along the hydrocarbon chain of a donor alkene (**1a**), accessing various alkylnickel(I) species (**II**) as latent radical equivalents, with which an electron-deficient CF_3-substituted olefin (**2a**) could act both as a ligand to stabilize the alkylnickel(I) species (**II**) and as a competent radical acceptor. The more stable alkyl radical, the radical cage pair (**IV**) generated by a single electron transfer of complex **III** will be selectively captured by the Ni(0)/**2a** complex to generate the nickel(I) species (**V**) which is expected to rapidly undergo β-fluorine elimination to deliver the desired product (**3a**). With a stoichiometric hydrosilane, the NiH species (**I**) is regenerated from NiF (**VI**) to complete the catalytic cycle.

On the basis of our previously developed NiH-catalyzed migratory hydrofunctionalization of olefins with electrophilic coupling partners,[10e,h,i,m–o,r] we first examined the proposed migratory defluorinative cross olefin-coupling of a 1,1-disubstituted alkene (**1a**) with a trifluoromethyl alkene (**2a**). Systematic manipulation of the reaction parameters revealed conditions under which the desired *gem*-difluoroalkene product (**3a**) was obtained in 73% isolated yield as a single regioisomer (Table 1, entry 1). Lower yield was obtained when using $NiBr_2$ as precatalyst (entry 2). The alkyl groups of **L1** were found to be critical and use of a parent pyridine compound, a 6,6'-dimethoxy derivative, or a 6,6'-ditrifluoromethyl derivative delivered little or no desired product (entries 3, 4). Replacement of **L1** with a C6-substituted pyrox ligand (**L5**) also gave no desired product (entry 4). Inferior results were achieved by other 6,6'-dialkylsubstituted pyridine-based ligands (**L2**, **L6**, entries 5, 6), and use of diethoxy(methyl)silane (DEMS) also resulted in decreased yield (entry 7). Control experiments revealed that base was critical (entry 8), and use of Li_2CO_3 was less efficient (entry 9). *N*,*N*-dimethylacetamide (DMA) was shown to be an unsuitable solvent (entry 10) and conduction of the reaction at 25 °C led to a poor yield (entry 11). In addition, the reaction is compatible with air and moisture; comparable yields were obtained when conducting the reaction under air in a closed vial and with 1.0 equiv water, respectively (entries 12, 13).

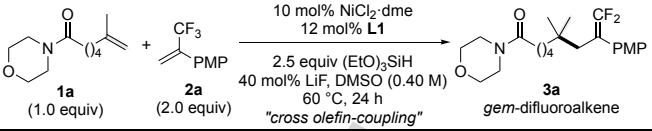
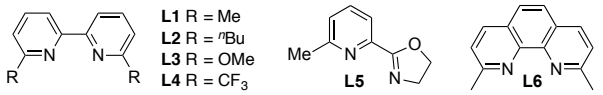


Table 1: Variation of reaction parameters.

Entry	Variation from standard conditions	Yield (%)[a]	rr[b]
1	none	80(73)	>99:1
2	$NiBr_2$ instead of $NiCl_2$·dme	64	>99:1
3	bpy instead of **L1**	<5	–
4	**L3**–**L5** instead of **L1**	0	–
5	**L2** instead of **L1**	29	>99:1
6	**L6** instead of **L1**	56	>99:1
7	DEMS instead of $(EtO)_3SiH$	70	>99:1
8	w/o LiF	4	–
9	Li_2CO_3 instead of LiF	65	>99:1
10	DMA instead of DMSO	18	>99:1
11	25 °C	12	>99:1
12	under air in a closed vial	77	>99:1
13	1.0 equiv water added	80	>99:1



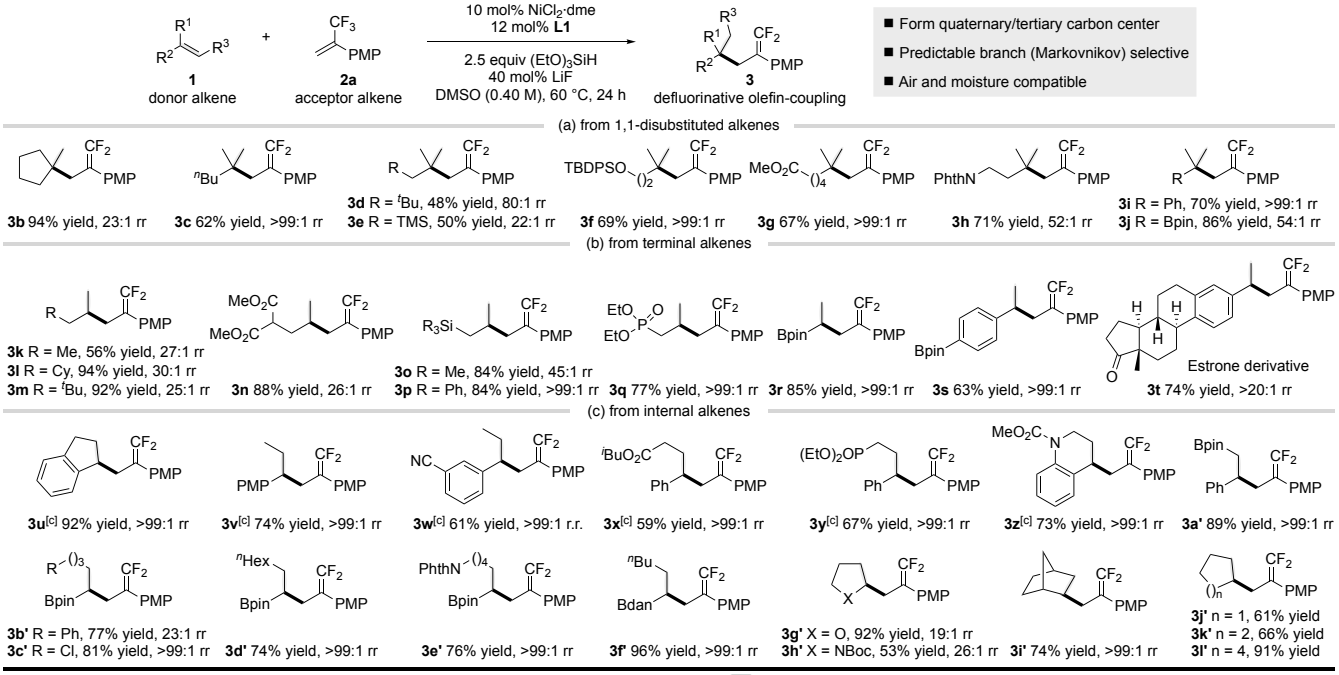
[a] Yields determined by GC using *n*-tetradecane as the internal standard, the yield in parentheses is the isolated yield. [b] Regioselectivities (rr) determined by GC and GCMS analysis. DMSO=dimethylsulfoxide.

With the optimal conditions in hand, we examined the scope of the donor alkene partner (Table 2). As anticipated, 1,1-disubstituted alkenes bearing a wide variety of substituents (**1a**–**1j**) underwent this transformation smoothly to form quaternary carbon compounds with excellent branch regioselectivity,[14] and a number of monosubstituted terminal alkenes (**1k**–**1t**) are compatible. In general, coupling occurs at the most accessible steric branch position and the formal defluorinated olefin-coupling product is formed. Both activated terminal and internal alkenes, such as styrenes (**1s**–**1a'**) and alkenyl boronic esters (**1r**, **1b'**–**1f'**), selectively couple at the benzylic position and α-carbon of the boronate, respectively. In addition, heteroatom substituted cyclic olefins, 2,3-dihydrofuran (**1g'**) and *N*-Boc-3-pyrroline (**1h'**) couple at the carbon α to the heteroatom. Coupling of simple cyclic olefins (**1i'**–**1l'**) is equally useful. Notably, a diverse spectrum of functional groups, including silanes (**1e**, **1o**, and **1p**), a silyl ether (**1f**), esters (**1g**, **1n**, and **1x**), phthalimides (**1h**, **1e'**), boronic esters (**1j**, **1r**, **1s**, and **1a'**–**1f'**), phosphate esters (**1q**, **1y**), a ketone (**1t**), a nitrile (**1w**), carbamates (**1z**, **1h'**), and an ether (**1g'**), are compatible.

As shown in Table 3a, in unactivated terminal (**4a**–**4k**) or internal (**4l**–**4n**) alkenes with a remote aryl group on the alkyl chain, migration toward the aryl group and subsequent benzylic coupling is preferred. To get better yields, Li_2CO_3 is used as base and DMA is chosen as solvent in most cases. As anticipated, a variety of substituents on the remote aryl ring, including electron donating (**4c**, **4d**) and electron withdrawing (**4f**–**4h**) substituents, are well tolerated. Notably, the reaction is orthogonal to tosylate (**4e**), aryl chloride (**4h**), and aryl fluoride (**4k**) which are potential coupling motifs that could be used for further derivatization. This method is also applicable to late-stage functionalization of a variety of structurally complex olefin intermediates, such as a (-)-camphanic acid (**4i**) derivative and a glucoside derivative (**4j**). Moreover, in remote alkenes with a

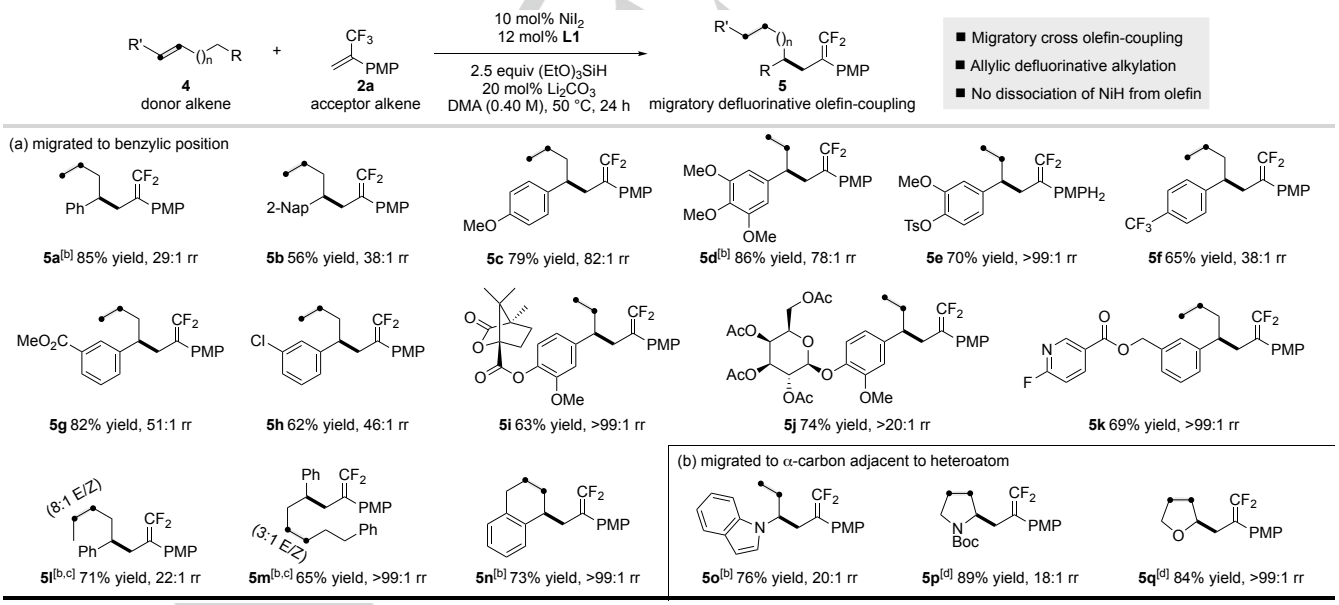
heteroatomic substituent at the terminus of the hydrocarbon chain, migratory coupling selectively happens at the carbon α to the heteroatom (**4o**–**4q**, Table 3b).

Table 2: Cross olefin-coupling: scope of alkene component.[a,b]



[a] Isolated yields on 0.20 mmol scale (average of two runs). [b] Rr determined by GC and GCMS analysis, ratios reported as >20:1 determined by crude ^{1}H NMR analysis. [c] 10 mol% $NiBr_2·3H_2O$, 12 mol% **L1**, 5 mol% PPh_3, 2.5 equiv $(EtO)_3SiH$, 40 mol% LiF, 20 mol% TBAB, DMA (0.40 M), 60 °C, 24 h. TBAB=tetrabutylammonium bromide.

Table 3: Migratory olefin-coupling: scope of alkene component.[a]

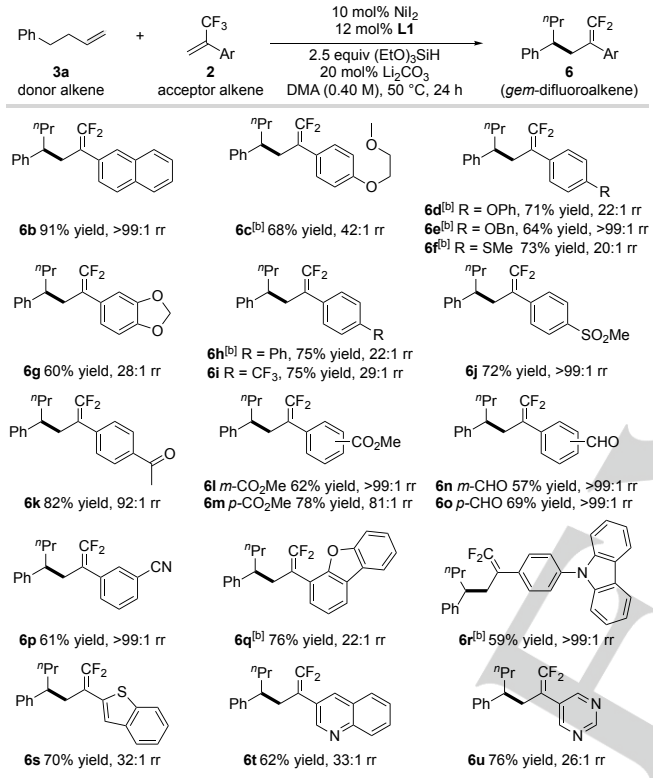


[a] Yield and rr are as defined in Table 2. [b] 10 mol% $NiBr_2·3H_2O$, 12 mol% **L1**, 5 mol% PPh_3, 2.5 equiv $(EtO)_3SiH$, 40 mol% LiF, 20 mol% TBAB, DMA (0.40 M), 60 °C, 24 h. [c] 1.0 equiv LiF used. [d] 10 mol% $NiCl_2·dme$, 12 mol% **L1**, 2.5 equiv $(EtO)_3SiH$, 40 mol% LiF, DMSO (0.40 M), 60 °C, 24 h.

The optimized conditions also prove to be efficient for various aryl and heteroaryl substituted trifluoromethyl alkenes

(Table 4). In terms of electronic properties, substrates with electron-rich (**2c**–**2e**) or electron-withdrawing (**2g**–**2o**) substituents on the aryl ring couple efficiently. Under these mild conditions, not only ethers (**2c**–**2g**), esters (**2l** and **2m**), and a nitrile (**2p**), are tolerated, even normally easy reduced functional groups like a sulfone (**2j**), a ketone (**2k**), and aldehydes (**2n**, **2o**) remain intact. Additionally, heterocycles such as a dibenzofuran (**2q**), a carbazole (**2r**), a benzothiophene (**2s**), a quinoline (**2t**), and a pyridine (**2u**) are also compatible. Unfortunately, alkyl-substituted trifluoromethyl alkenes are inactive under current conditions.

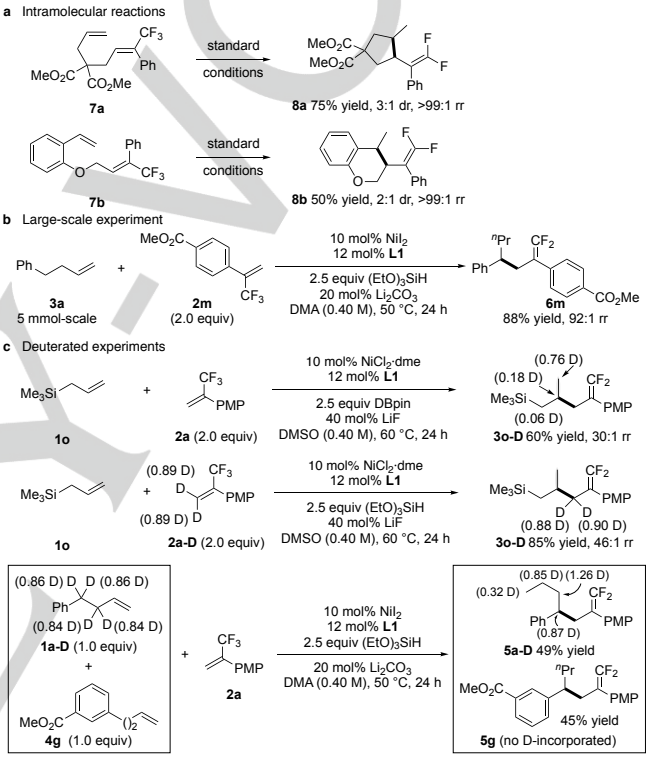
Table 4: Scope of the trifluoromethyl alkene component.[a]



[a] Yield and rr are as defined in Table 2. [b] 10 mol% $NiBr_2 \cdot 3H_2O$, 12 mol% **L1**, 5 mol% PPh_3, 2.5 equiv $(EtO)_3SiH$, 40 mol% LiF, 20 mol% TBAB, DMA (0.40 M), 60 °C, 24 h.

This process also proceeds well in an intramolecular version (Scheme 1a). Under the standard conditions, reductive defluorinative cyclization products (**8a**, **8b**) are obtained as single regioisomers. The robustness and applicability of this process was further demonstrated by the large-scale synthesis of **6m** (Scheme 1b).

As shown in Scheme 1c, a series of isotope labeling experiments were conducted in an effort to understand the behavior of NiH. A reaction of allyltrimethylsilane (**1o**) with a trifluoromethyl olefin (**2a**) using a deuterated pinacolborane (DBpin) as the hydride source was first carried out. The corresponding product **3o-D** was obtained with deuterium scrambling and deuterium incorporation only at all positions along the hydrocarbon chain of donor alkene. This is consistent with the hypothesis that NiH-catalyzed chainwalking selectively occurs with a donor alkene (**1o**) over the acceptor alkene (**2a**). Moreover, that no deuterium scrambling occurred when a deuterated trifluoromethyl olefin (**2a-D**) was used further supports that there is no chainwalking along the acceptor olefin (**2a**). Finally, a crossover reaction was carried out with equimolar amounts of deuterated olefin (**1a-D**) and undeuterated olefin (**4g**). Interestingly, **5a-D** and **5g** were obtained as the only products and no crossover product **5g-D** was observed. This observation indicates that chainwalking occurs without dissociation of NiH/NiD from the donor olefin, which stands in contrast to our previously studied processes.[10e,h,i,m–o,r]



Scheme 1. Intramolecular, large-scale, and deuterated experiments.

In summary, we have developed a NiH-catalyzed migratory defluorinative olefin-coupling of unactivated donor olefins with CF_3-substituted acceptor olefins, both intra- and intermolecularly to form *gem*-difluoroalkenes. This mild process is compatible with air and moisture and has broad substrate scope. Excellent chemo- and regioselectivity are observed with the formation of a tertiary or quaternary carbon center. Further development and application of this reaction as well as mechanistic investigation is currently in progress.

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Keywords: C–H activation • cross-coupling • isomerization • nickel • regioselectivity

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[14] The major byproduct is the corresponding difluoroalkene generated via competitive hydrodefluorination of acceptor alkene.

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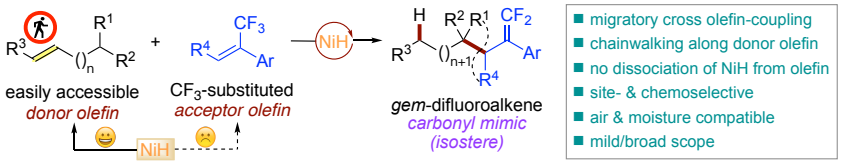
Layout 2:

COMMUNICATION



gem-Difluoroalkenes, a carbonyl bioisostere in modern drug discovery, were obtained through a practical migratory defluorinative cross olefin-coupling process between donor olefin and trifluoromethyl-substituted acceptor olefin. During this mild process, chainwalking occurs only along the hydrocarbon chain of the donor olefin with no dissociation of NiH.

*Fenglin Chen, Xianfeng Xu, Yuli He, Genping Huang, and Shaolin Zhu**

Page No. – Page No.

NiH-Catalyzed Migratory Defluorinative Cross Olefin-Coupling: Trifluoromethyl-Substituted Alkenes as Acceptor Olefins to Form *gem*-Difluoroalkenes