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Communication

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Enantioselective Three-Component Fluoroalkylarylation of Unactivated Olefins Through Nickel-Catalyzed Cross-Electrophile Coupling

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Supporting Information Placeholder

ABSTRACT: A nickel-catalyzed, enantioselective, three-component fluoroalkylarylation of unactivated alkenes with aryl halides and perfluoroalkyl iodides has been described. This cross-electrophile coupling protocol utilizes a chiral nickel/BiOx system as well as a pendant chelating group to facilitate the challenging three-component, asymmetric difunctionalization of unactivated alkenes, providing direct access to valuable chiral β-fluoroalkyl arylalkanes with high efficiency and excellent enantioselectivity. The mild conditions allow for a broad substrate scope as well as good functional group toleration.

Transition metal-catalyzed dicarbofunctionalization of alkenes has been proven as a powerful strategy to the rapid generation of molecular complexity by simultaneously forging two vicinal sp^3 C–C bonds from abundant building blocks in one single operation;[1] however, enantioselective control of the newly formed stereogenic centers,[2] particularly in three-component assembly mode, remains a formidable challenge. The known examples of three-component reactions densely rely on the asymmetric functionalization of vinylarenes via a radical relay strategy, wherein intercepting the putative benzylic radicals by chiral transition metal catalysts is key.[3, 4] Nevertheless, unactivated alkenes were not applicable in this asymmetric radical protocol, presumably because of lacking resonance stabilization for the *in-situ* generated highly reactive alkyl radical species. Indeed, asymmetric dicarbofunctionalization of unactivated alkenes has been primarily restricted to intramolecular, two-component assembly modes.[5] To the best of our knowledge, catalytic, enantioselective, three-component difunctionalization of unactivated alkenes has not been reported. Herein, we report an enantioselective 1,2-fluoroalkylarylation of unactivated alkenes with aryl halides and perfluoroalkyl iodides through a chelation-assisted nickel-catalyzed cross-electrophile coupling[6], which demonstrates an example of the integration of three-component dicarbofunctionalization of unactivated alkenes with a high level of enantioselectivity for the first time.

Owing to the unique properties of nickel catalysts,[7] recently, several research groups, including ours, have established that nickel could enable three-component cross-coupling reactions of unactivated alkenes, forging two consecutive sp^3-hybridized carbon centers, with one sp^3 prochiral center.[8, 9] With a particular interest in the introduction of fluoroalkyl groups because of their increasing importance in medicinal agents,[10] as well as the high reactivity of perfluoroalkyl radicals,[11] our group previously developed an intermolecular, selective carboacylation of unactivated alkenes with acyl chlorides and perfluoroalkyl halides via a Ni-catalyzed cross-electrophile coupling, incorporating the perfluoroalkyl and carbonyl groups over unbiased double bonds under mild conditions.[8j] In this work, a weak coordination effect between the pendant chelating group and nickel species was found to be crucial to achieving the challenging regio- and chemo-selectivity in three-component cross-coupling reactions. Encouraged by these results, we envisioned that whether it would be possible to use a chiral ligand, assisted by a proper pendant

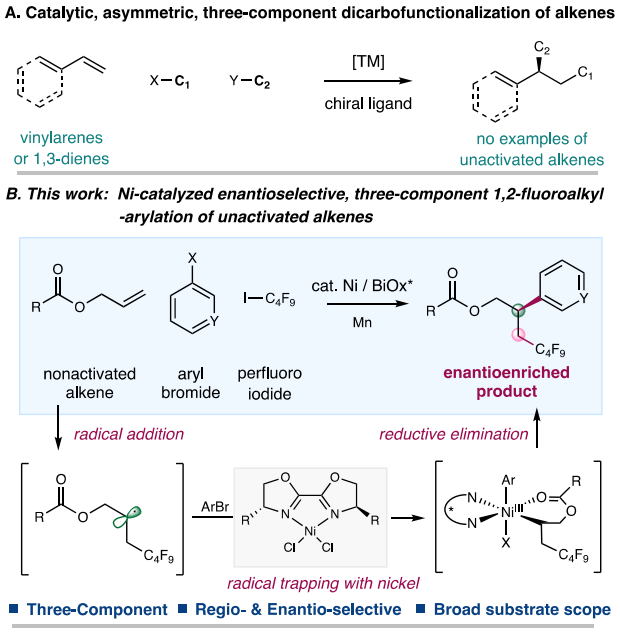
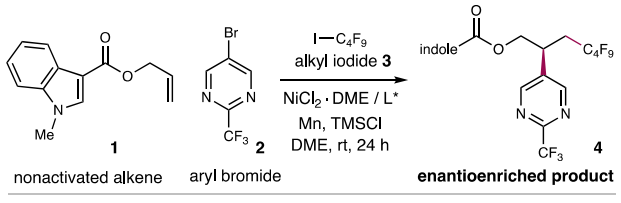
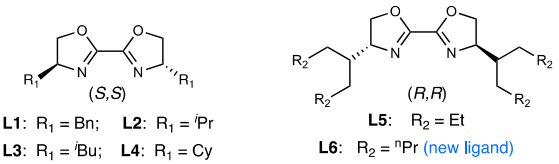


Figure 1. Enantioselective, three-component 1,2-fluoroalkylarylation of unactivated alkenes via chelation-assisted nickel catalysis.

Table 1. Optimization of reaction conditions[a]





entry	variations from standard conditions	yield	er
1	**L1**	21%	20:80
2	**L2**	55%	12:88
3	**L3**	24%	10:90
4	**L4**	75%	9:91
5	**L5**	87%	94:6
6	**L6**	81%	94:6
7	-10 °C, instead of rt	76%	95:5
8	Zn or TDAE, instead of Mn	trace	--
9	w/o nickel, **L5**, or Mn	0%	--
10	w/o TMSCl	66%	93:7

[a]Reactions were carried out with alkene **1** (0.2 mmol), aryl bromide **2** (0.1 mmol), C_4F_9I (0.2 mmol), $NiCl_2$•glyme (10 mol%), chiral ligand (12 mol%), TMSCl (0.01 mmol), Mn (0.25 mmol), DME [0.5 M], rt, 24 h. Yields were determined by GC using an internal standard. The er values were determined by HPLC on a chiral stationary phase.

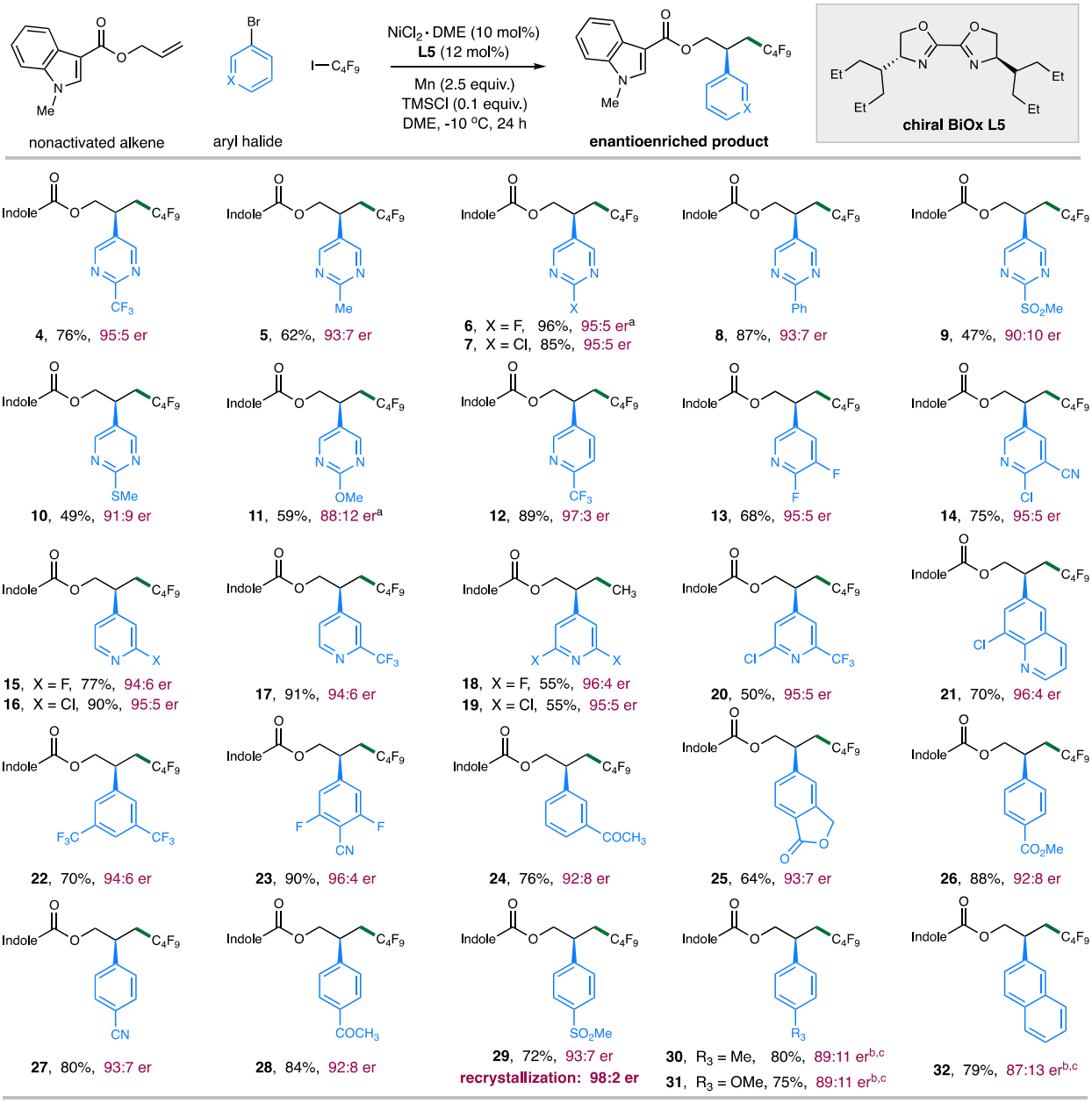
directing group, to facilitate the stereocontolled radical/nickel combination step, thus fulfilling catalytic enantioselective control in the intermolecular three-component version of unactivated alkenes.

With this idea in mind, we began our investigations by evaluating unactivated alkenes incorporated with different types of directing groups. Pleasingly, we found that allylic ester, the carbonyl group of which could interact with nickel species via a six-membered-chelated ring, was a promising non-conjugated alkene substrate for this enantioselective, three-component dicarbofunctionalization reaction (See Table S1). Employing the catalyst combination of $NiCl_2$•DME and chiral bioxazoline (Bn-BiOX, **L1**), reaction of allyl ester **1** with 5-bromo-2-(trifluoromethyl)pyrimidine **2** and C_4F_9I in the presence of stoichiometric Mn and catalytic TMSCl afforded the desired 1,2-fluoroalkylarylation product **4** in 21% yield with an encouraging 20:80 (*S:R*) enantiomeric ratio (er) (Table 1, entry 1). Several pendant directing groups such as carbonates, carbamates and benzoates, afforded decreased ers with varied yields (Table S1). Screening of chiral ligands indicated that only BiOx ligands[4d, 6e, 6h] were effective, while other commonly employed chiral ligands all failed to promote this three-component reaction under similar conditions (Table S2 and S7). Therefore, we further screened a series of chiral BiOx ligands, and found that BiOx ligands containing longer alkyl chains offered higher yield and enantioselectivity, and (*R*,*R*)-4-heptyl-BiOX (**L5**), originally developed for Ni-catalyzed asymmetric reductive cross-couplings,[6e, 6h] delivered product **4h** with 87% yield and 94:6 er at room temperature (entries 2–5). Encouraged by this result,[6h] we designed and synthesized a new (*R*,*R*)-5-nonyl-BiOX ligand (**L6**) bearing alkyl chains with nine carbon atoms, which to our disappointment provided the same er with **L5** (entry 6). Finally, conducting the reaction at lower temperature (–10 °C) slightly improved enantioselectivity, furnishing **4** with 95:5 er in 76% yield (entry 7). A trace amount of product was observed when employing Zn or TDAE (tetrakis(dimethylamino)ethylene)[12] as a stoichiometric reductant (entry 8). Control experiments further confirmed that all nickel catalyst, ligand, and Mn dust were required for this asymmetric system (entry 9). Employment of TMSCl, which could activate the surface of Mn, as additive was important to ensure reproducibility for this transformation (entry 10) (See Table S1–S11 for more optimizations).

With optimal reaction conditions in hand, we began to explore the generality of this asymmetric, three-component 1,2-fluoroalkylarylation of unactivated alkenes with respect to aryl and heteroaryl halides. As shown in Scheme 1, a variety of 5-bromopyrimidines bearing electron-withdrawing and electron-donating groups all underwent the desired cross-electrophile coupling smoothly, delivering the corresponding chiral β-fluoroalkyl arylalkanes with good to excellent yields and high enantioselectivity (Products **4**–**11**, 47%–96% yields, up to 95:5 er); while pyrimidines with electron-donating groups displayed lower efficiency (Products **10** and **11**). Moreover, electron-deficient pyridines and quinolines were also viable coupling partners, furnishing 1,2-fluoroalkylarylation products in good yields and high ers (Products **12**–**21**, 50%–91% yields, up to 97:3 er). It should be noted that ortho-substituents in pyrimidines and pyridines were found to be crucial to achieving high enantioselective control in this transformation, and simple 2-bromopyridine was ineffective under the standard conditions. We surmised that the presence of 2-substituent would prevent the undesired coordination between nickel and nitrogen atom of heterocycles. Additionally, this catalytic protocol demonstrated excellent chemoselectivity, as exclusive reactivity toward bromides over chlorides was observed in the cases of multiple halogenated heteroarenes (Products **7**, **14**, **16**, **19**–**21**). Moreover, electron-deficient aryl bromides also worked well to give the three-component coupling products in good yields and high ers (Products **26**–**29**, 72%–88% yields, up to 98:2 er). Notably, simple recrystallization from hot ethanol furnished product **29** in 96% ee. The mild reaction conditions were well compatible with a wide range of important functionalities, including CF_3, chloride, thioether, sulfone, cyano, ketone, and ester, offering useful handles for further synthetic manipulations (Products **4**–**29**). Nevertheless, electron-neutral and -rich aryl iodides showed lower reactivity in this catalytic protocol, furnishing the final

products with moderate yields and ers (Products **30**–**32**, 75%–80% yields, up to 89:11 er).

1-chloro-2-iodotetrafluoroethane proceeded smoothly to afford product **39**, via selective cleavage of C–I bond, in 66%

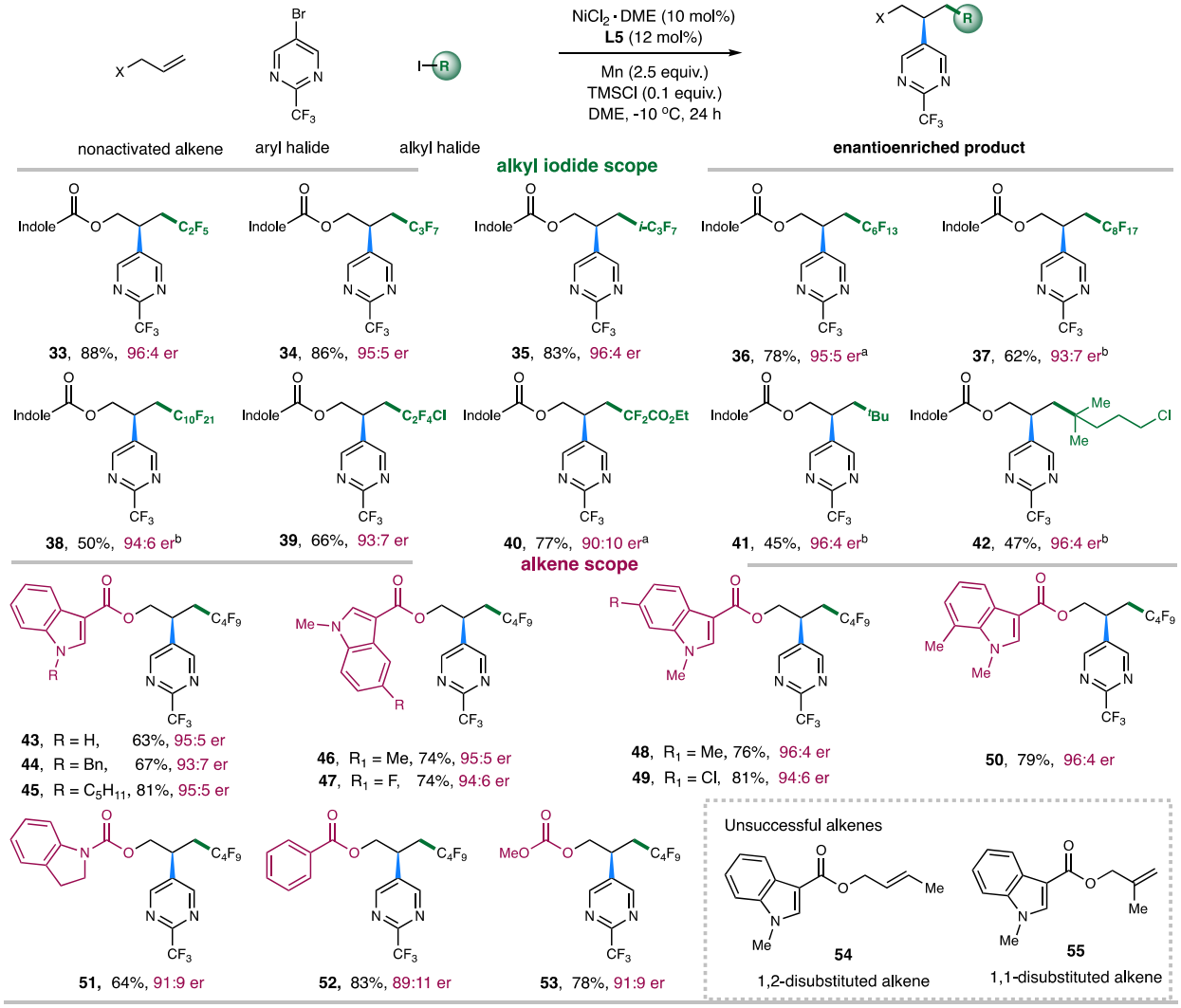


Scheme 1. Scope of aryl halides. Reaction conditions: alkene **1** (0.2 mmol), aryl bromide (0.1 mmol), C_4F_9I (0.2 mmol), $NiCl_2$•glyme (10 mol%), **L5** (12 mol%), TMSCl (0.01 mmol), Mn (0.25 mmol), DME [0.5 M], -10 °C, 24 h. Isolated yields. The er values were determined by HPLC on a chiral stationary phase. [a]Conducted at 0 °C. [b]Conducted at room temperature. [c]With aryl iodide. Indole = 1-methyl-1*H*-indole.

Next, we examined the scope of the fluoroalkyl precursors. As depicted in Scheme 2, a wide array of perfluoroalkyl iodides (from C_2 to C_{10}) could be employed as competent C-radical precursors, leading to the corresponding enantioenriched fluoroalkyl-containing motifs in moderate to high yields and high ers (Products **33**–**38**, 50%–88% yields, up to 96:4 er). While reaction efficiency decreased to a small extent as the fluoroalkyl carbon chains grew longer, probably due to the lower solubility of larger perfluoroalkyl iodides in the current system (Products **37** and **38**). The reaction with

yield and 93:7 er. Moreover, ethyl difluoroiodoacetate also underwent this asymmetric three-component protocol smoothly (Product **40**, 77% yield, 90:10 er). Pleasingly, we also found that tertiary alkyl iodides could be employed as effective nonfluorinated C-radical precursors to afford the 1,2-alkylarylated products **41** and **42** with 96:4 ers, albeit in relatively low yields (45% and 37% yield, respectively).[13]

Finally, we also examined the reactivity of unactivated alkenes under the optimal conditions (Scheme 2). Allyl esters derived from different indole-3-carboxylic acids all



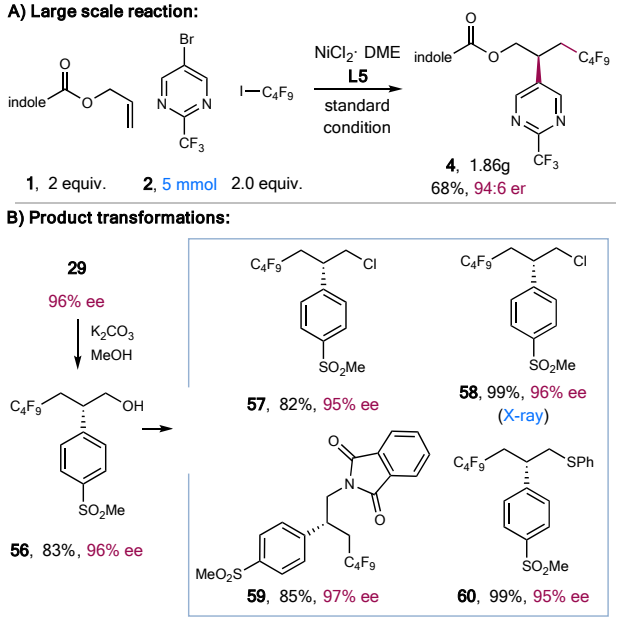
Scheme 2. Scope of alkenes and alkyl halides. Reaction conditions: alkene (0.2 mmol), aryl bromide (0.1 mmol), alkyl halide (0.2 mmol), $NiCl_2$•glyme (10 mol%), **L5** (12 mol%), TMSCl (0.01 mmol), Mn (0.25 mmol), DME [0.5 M], -10 °C, 24 h. Isolated yields. The er values were determined by HPLC on a chiral stationary phase. [a]Conducted at 0 °C. [b]Conducted at room temperature. Indole = 1-methyl-1*H*-indole

underwent the desired three-component coupling reaction in good yields and high ers (Products **43**–**50**, 63%–81% yields, up to 96:4 er). Substituents on nitrogen atom or the indole ring had no significant influence on the yield and enantioselectivity of this transformation. Unprotected indole was also well-tolerated under mild conditions (Product **43**). Interestingly, allyl esters incorporating other types of directing groups, exemplified by benzoate, carbonate, and carbamate, were also applicable in this system, albeit with only moderate enantioselectivity (Products **51**–**53**, 64%–83% yields, up to 91:9 er). Nevertheless, 1,1-disubstituted alkenes and 1,2-disubstituted internal alkenes were generally ineffective (e.g. **54** and **55**).

This asymmetric, three-component difunctionalization protocol could be feasibly scaled up, yield and enantioselectivity of product **4** on a gram scale were comparable to a smaller scale (Scheme 3A). Furthermore, the ester directing group of product **29** could be easily cleavage via K_2CO_3 in MeOH,[14] affording the enantioenriched γ-fluoroalkyl-β-aryl alcohol **56** (96% ee) without racemization (Scheme 3B). To further demonstrate the synthetic utility of this asymmetric method, several diversifications of alcohol **56** were performed (Scheme 3B). γ-Fluoroalkyl alcohol was easily converted to the corresponding alkyl chloride **57** (95% ee) and bromide **58** (96% ee),[15] versatile intermediates in organic synthesis, in high yields without loss of enantioselectivity. Substitutions of **56** with phenyl disulfide and phthalimide afforded fluoroalkyl thiol **60** (95% ee) and fluoroalkyl amide **59** (97% ee) in 99% and 85% yields,[16] respectively. It should be noted that the absolute configuration of compound **58** was assigned by X-ray diffraction analysis and the configuration of the other products was assigned by analogy (see SI for X-ray diffraction data for **58**).

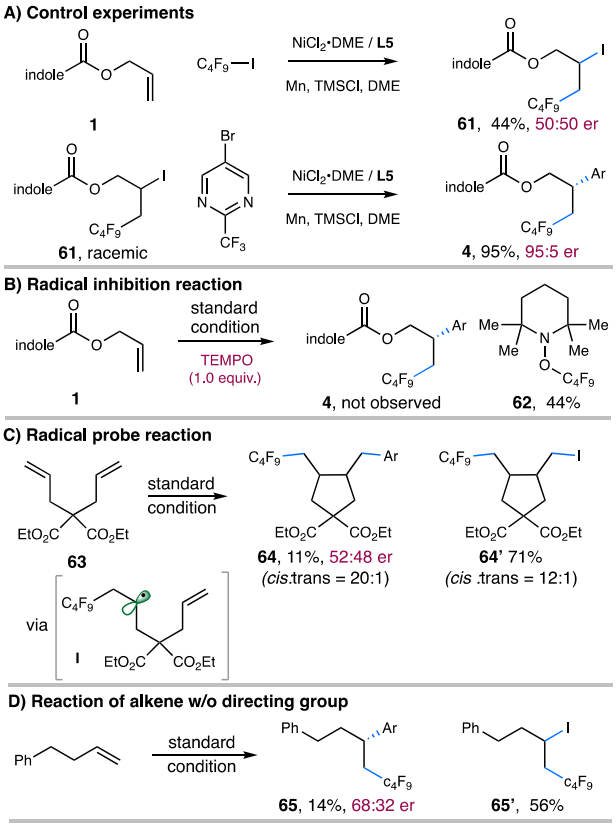
To shed some light on the plausible mechanism of this novel nickel-catalyzed enantioselective three-component

fluoroalkylarylation reaction, we have conducted several preliminary mechanistic experiments (Scheme 4). Since the iodoperfluoroalkylation byproduct was detected in our reactions,[17] we performed a control reaction of alkene **1** with C_4F_9I in the absence of aryl bromide, which gave the racemic



Scheme 3. A) Large scale reaction; B) Cleavage of directing group and product transformations. a. CCl_4, PPh_3, CH_2Cl_2; b. CBr_4, PPh_3, CH_2Cl_2; c. PhSSPh, PBu_3, THF; d. phthalimide, PPh_3, DIAD, THF.

alkyl iodide **61** in 44% yield (Scheme 4A). Two-component reaction of racemic **61** with aryl bromide **2** in the presence of Ni(II)/(*R,R*)-**L5** and Mn also furnished product **4** with excellent yield and enantioselectivity (Scheme 4A).[18] Moreover, the time courses for this reaction disclosed that the conversion of alkene **1** into alkyl iodide **61** was achieved at the beginning of the reaction, and then the final product **4** gradually formed as the consumption of intermediate **61**, suggesting alkyl iodide was an on-cycle reactive intermediate in this catalytic system (Fig. S1). On the other hand, the desired reaction was completely inhibited by TEMPO, and TEMPO-C_4F_9 adduct **62** was observed via ^{19}F NMR (Scheme 4B). The radical probe reaction of diene **63** with aryl bromide **2** and C_4F_9I resulted in the cyclized product **64** in 11% yield (*cis/trans* 20:1, 52:48 er)[19] along with 71% yield of the cyclized alkyl iodide **64'** (*cis/trans* 12:1)[20] (Scheme 4C). These cis/trans ratios were consistent with the involvement of a radical intermediate (Scheme 4C).[9a, 19, 21] To further diagnose the importance of chelation effect for this remarkable enantioselective control, we submitted 4-phenyl-1-butene, a non-activated alkene without a chelation group, into our standard condition, which only afforded the desired product **65** in 14% yield and 68:32 er, along with 56% yield of alkyl iodide **65'** (Scheme 4D). We anticipated that the weak chelating effect of the pendant indole carbonate group would be beneficial to the enantio-determining step of this



Scheme 4. Preliminary mechanistic studies.

transformation.[22] Nevertheless, further studies are required to fully elucidate the possible reaction pathway.[9f, 23]

In conclusion, we have developed the first enantioselective, three-component 1,2-fluoroalkylarylation of unactivated alkenes with aryl halides and fluoroalkyl iodides via a chelation-assisted Ni-catalyzed multicomponent cross-electrophile coupling. The benign protocol allows for the facile construction of a wide range of functionalized chiral β-fluoroalkyl arylalkanes with high efficiency and excellent enantioselectivity from readily available starting materials. The pendant ester group plays a crucial role in achieving high levels of enantioselectivity and efficiency in this three-component, asymmetric difunctionalization of unactivated alkenes. Moreover, the chelating group could be readily cleaved to give enantioenriched alcohols, further transformations of which generate a series of chiral fluoroalkyl-containing motifs that could be useful in the areas of pharmaceuticals and agrochemicals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

- Experimental details, analytical data, and NMR spectra for all new compounds; synthetic applications; effect of reaction parameters; mechanistic studies (PDF)
- X-ray crystallographic details for Compound **58** (CIF)

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REFERENCES

1. For selected reviews, see: (a) Merino, E.; Nevado, C., Addition of CF3 across unsaturated moieties: a powerful functionalization tool. *Chem. Soc. Rev.* **2014**, *43* (18), 6598-6608; (b) Dhungana, R. K.; KC, S.; Basnet, P.; Giri, R., Transition Metal-Catalyzed Dicarbofunctionalization of Unactivated Olefins. *Chem. Rec.* **2018**, *18* (9), 1314-1340; (c) Giri, R.; Kc, S., Strategies toward Dicarbofunctionalization of Unactivated Olefins by Combined Heck Carbometalation and Cross-Coupling. *J. Org. Chem.* **2018**, *83* (6), 3013-3022; (d) Zhang, J.-S.; Liu, L.; Chen, T.; Han, L.-B., Transition-Metal-Catalyzed Three-Component Difunctionalizations of Alkenes. *Chem. Asian J.* **2018**, *13* (17), 2277-2291; (e) J. Derosa; V. T. Tran; V. A. van der Puyl; Engle, K. M., Carbon–Carbon π Bonds as Conjunctive Reagents in Cross-Coupling. *Aldrichimi. Acta* **2018**, *51*, 21-32; (f) Lin, J.; Song, R.-J.; Hu, M.; Li, J.-H., Recent Advances in the Intermolecular Oxidative Difunctionalization of Alkenes. *Chem. Rec.* **2019**, *19* (2-3), 440-451.
2. For selected reviews, see: (a) McDonald, R. I.; Liu, G.; Stahl, S. S., Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev.* **2011**, *111* (4), 2981-3019; (b) Coombs, J. R.; Morken, J. P., Catalytic Enantioselective Functionalization of Unactivated Terminal Alkenes. *Angew. Chem. Int. Ed.* **2016**, *55* (8), 2636-2649.
3. For recent examples on Cu-catalyzed three-component, asymmetric alkene difunctionalizations, see: (a) Wang, F.; Wang, D.; Wan, X.; Wu, L.; Chen, P.; Liu, G., Enantioselective Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes via Radical Process. *J. Am. Chem. Soc.* **2016**, *138* (48), 15547-15550; (b) Wu, L.; Wang, F.; Wan, X.; Wang, D.; Chen, P.; Liu, G., Asymmetric Cu-Catalyzed Intermolecular Trifluoromethylarylation of Styrenes: Enantioselective Arylation of Benzylic Radicals. *J. Am. Chem. Soc.* **2017**, *139* (8), 2904-2907; (c) Fu, L.; Zhou, S.; Wan, X.; Chen, P.; Liu, G., Enantioselective Trifluoromethylalkynylation of Alkenes via Copper-Catalyzed Radical Relay. *J. Am. Chem. Soc.* **2018**, *140* (35), 10965-10969; (d) Wang, F.; Chen, P.; Liu, G., Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51* (9), 2036-2046; (e) Wu, L. Q.; Wang, F.; Chen, P. H.; Liu, G. S., Enantioselective Construction of Quaternary All-Carbon Centers via Copper-Catalyzed Arylation of Tertiary Carbon-Centered Radicals. *J. Am. Chem. Soc.* **2019**, *141* (5), 1887-1892; (f) Lin, J.-S.; Li, T.-T.; Liu, J.-R.; Jiao, G.-Y.; Gu, Q.-S.; Cheng, J.-T.; Guo, Y.-L.; Hong, X.; Liu, X.-Y., Cu/Chiral Phosphoric Acid-Catalyzed Asymmetric Three-Component Radical-Initiated 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019**, *141* (2), 1074-1083; (g) Sha, W.; Deng, L.; Ni, S.; Mei, H.; Han, J.; Pan, Y., Merging Photoredox and Copper Catalysis: Enantioselective Radical Cyanoalkylation of Styrenes. *ACS Catal.* **2018**, *8* (8), 7489-7494; (h) Zhang, Z. Q.; Meng, X. Y.; Sheng, J.; Lan, Q.; Wang, X. S., Enantioselective Copper-Catalyzed 1,5-Cyanotrifluoromethylation of Vinylcyclopropanes. *Org. Lett.* **2019**, *21* (20), 8256-8260.
4. For recent examples on catalytic, three-component, asymmetric alkene difunctionalizations enabled by other metals, see: (a) Stokes, B. J.; Liao, L.; de Andrade, A. M.; Wang, Q.; Sigman, M. S., A Palladium-Catalyzed Three-Component-Coupling Strategy for the Differential Vicinal Diarylation of Terminal 1,3-Dienes. *Org. Lett.* **2014**, *16* (17), 4666-4669; (b) Gu, J.-W.; Min, Q.-Q.; Yu, L.-C.; Zhang, X., Tandem Difluoroalkylation-Arylation of Enamides Catalyzed by Nickel. *Angew. Chem. Int. Ed.* **2016**, *55* (40), 12270-12274; (c) Xiong, Y.; Zhang, G., Enantioselective 1,2-Difunctionalization of 1,3-Butadiene by Sequential Alkylation and Carbonyl Allylation. *J. Am. Chem. Soc.* **2018**, *140* (8), 2735-2738; (d) Anthony, D.; Lin, Q.; Baudet, J.; Diao, T., Nickel-Catalyzed Asymmetric Reductive Diarylation of Vinylarenes. *Angew. Chem. Int. Ed.* **2019**, *58* (10), 3198-3202.
5. (a) Watson, M. P.; Jacobsen, E. N., Asymmetric Intramolecular Arylcyanation of Unactivated Olefins via C–CN Bond Activation. *J. Am. Chem. Soc.* **2008**, *130* (38), 12594-12595; (b) You, W.; Brown, M. K., Catalytic Enantioselective Diarylation of Alkenes. *J. Am. Chem. Soc.* **2015**, *137* (46), 14578-14581; (c) Carmona, R. C.; Köster, O. D.; Correia, C. R. D., Chiral N,N Ligands Enabling Palladium-Catalyzed Enantioselective Intramolecular Heck-Matsuda Carbonylation Reactions by Sequential Migratory and CO Insertions. *Angew. Chem. Int. Ed.* **2018**, *57* (37), 12067-12070; (d) Wang, K.; Ding, Z.; Zhou, Z.; Kong, W., Ni-Catalyzed Enantioselective Reductive Diarylation of Activated Alkenes by Domino Cyclization/Cross-Coupling. *J. Am. Chem. Soc.* **2018**, *140* (39), 12364-12368; (e) Tian, Z. X.; Qiao, J. B.; Xu, G. L.; Pang, X.; Qi, L.; Ma, W. Y.; Zhao, Z. Z.; Duan, J.; Du, Y. F.; Su, P.; Liu, X. Y.; Shu, X. Z., Highly Enantioselective Cross-Electrophile Aryl-Alkenylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2019**, *141* (18), 7637-7643; (f) Jin, Y.; Wang, C., Nickel-Catalyzed Asymmetric Reductive Arylalkylation of Unactivated Alkenes. *Angew. Chem. Int. Ed.* **2019**, *58* (20), 6722-6726; (g) Li, Y.; Ding, Z.; Lei, A.; Kong, W., Ni-Catalyzed enantioselective reductive aryl-alkenylation of alkenes: application to the synthesis of (+)-physovenine and (+)-physostigmine. *Org. Chem. Front.* **2019**, *6* (18), 3305-3309; (h) Zhang, Z. M.; Xu, B.; Wu, L.; Wu, Y.; Qian, Y.; Zhou, L.; Liu, Y.; Zhang, J., Enantioselective Dicarbofunctionalization of Unactivated Alkenes by Palladium-Catalyzed Tandem Heck/Suzuki Coupling Reaction. *Angew. Chem. Int. Ed.* **2019**, *58* (41), 14653-14659.
6. For examples on Ni-catalyzed asymmetric reductive cross-couplings, see: (a) Zhao, Y.; Weix, D. J., Enantioselective Cross-Coupling of meso-Epoxides with Aryl Halides. *J. Am. Chem. Soc.* **2015**, *137* (9), 3237-3240; (b) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E., Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α-Disubstituted Ketones. *J. Am. Chem. Soc.*

2013, *135* (20), 7442-7445; (c) Cherney, A. H.; Reisman, S. E., Nickel-Catalyzed Asymmetric Reductive Cross-Coupling Between Vinyl and Benzyl Electrophiles. *J. Am. Chem. Soc.* **2014**, *136* (41), 14365-14368; (d) Kadunce, N. T.; Reisman, S. E., Nickel-Catalyzed Asymmetric Reductive Cross-Coupling between Heteroaryl Iodides and α-Chloronitriles. *J. Am. Chem. Soc.* **2015**, *137* (33), 10480-10483; (e) Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E., Nickel-Catalyzed Asymmetric Reductive Cross-Coupling To Access 1,1-Diarylalkanes. *J. Am. Chem. Soc.* **2017**, *139* (16), 5684-5687; (f) Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E., Nickel-Catalyzed Enantioselective Cross-Coupling of N-Hydroxyphthalimide Esters with Vinyl Bromides. *Org. Lett.* **2017**, *19*, 2150-2153; (g) Hofstra, J. L.; Cherney, A. H.; Ordner, C. M.; Reisman, S. E., Synthesis of Enantioenriched Allylic Silanes via Nickel-Catalyzed Reductive Cross-Coupling. *J. Am. Chem. Soc.* **2018**, *140* (1), 139-142; (h) Woods, B. P.; Orlandi, M.; Huang, C. Y.; Sigman, M. S.; Doyle, A. G., Nickel-Catalyzed Enantioselective Reductive Cross-Coupling of Styrenyl Aziridines. *J. Am. Chem. Soc.* **2017**, *139* (16), 5688-5691.

7. For selected reviews, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F., Recent advances in homogeneous nickel catalysis. *Nature* **2014**, *509*, 299; (b) Ananikov, V. P., Nickel: The "Spirited Horse" of Transition Metal Catalysis. *ACS Catal.* **2015**, *5* (3), 1964-1971; (c) Choi, J.; Fu, G. C., Transition metal–catalyzed alkyl-alkyl bond formation: Another dimension in cross-coupling chemistry. *Science* **2017**, *356* (6334), eaaf7230.

8. For recent examples on Ni-catalyzed three-component dicarbofunctionalizations of unactivated alkenes, see: (a) Shrestha, B.; Basnet, P.; Dhungana, R. K.; Kc, S.; Thapa, S.; Sears, J. M.; Giri, R., Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles. *J. Am. Chem. Soc.* **2017**, *139* (31), 10653-10656; (b) García-Domínguez, A.; Li, Z.; Nevado, C., Nickel-Catalyzed Reductive Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2017**, *139* (20), 6835-6838; (c) Derosa, J.; Tran, V. T.; Boulous, M. N.; Chen, J. S.; Engle, K. M., Nickel-Catalyzed β,γ-Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Conjunctive Cross-Coupling. *J. Am. Chem. Soc.* **2017**, *139* (31), 10657-10660; (d) Thapa, S.; Dhungana, R. K.; Magar, R. T.; Shrestha, B.; Kc, S.; Giri, R., Ni-catalysed regioselective 1,2-diarylation of unactivated olefins by stabilizing Heck intermediates as pyridylsilyl-coordinated transient metallacycles. *Chem. Sci.* **2018**, *9* (4), 904-909; (e) Basnet, P.; Dhungana, R. K.; Thapa, S.; Shrestha, B.; Kc, S.; Sears, J. M.; Giri, R., Ni-Catalyzed Regioselective beta,delta-Diarylation of Unactivated Olefins in Ketimines via Ligand-Enabled Contraction of Transient Nickellacycles: Rapid Access to Remotely Diarylated Ketones. *J. Am. Chem. Soc.* **2018**, *140* (25), 7782-7786; (f) Basnet, P.; Kc, S.; Dhungana, R. K.; Shrestha, B.; Boyle, T. J.; Giri, R., Synergistic Bimetallic Ni/Ag and Ni/Cu Catalysis for Regioselective gamma,delta-Diarylation of Alkenyl Ketimines: Addressing beta-H Elimination by in Situ Generation of Cationic Ni(II) Catalysts. *J. Am. Chem. Soc.* **2018**, *140* (46), 15586-15590; (g) Kc, S.; Basnet, P.; Thapa, S.; Shrestha, B.; Giri, R., Ni-Catalyzed Regioselective Dicarbofunctionalization of Unactivated Olefins by Tandem Cyclization/Cross-Coupling and Application to the Concise Synthesis of Lignan Natural Products. *J. Org. Chem.* **2018**, *83* (5), 2920-2936; (h) Derosa, J.; van der Puyl, V. A.; Tran, V. T.; Liu, M.; Engle, Keary M., Directed nickel-catalyzed 1,2-dialkylation of alkenyl carbonyl compounds. *Chem. Sci.* **2018**, *9* (23), 5278-5283; (i) Derosa, J.; Kleinmans, R.; Tran, V. T.; Karunananda, M. K.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M., Nickel-Catalyzed 1,2-Diarylation of Simple Alkenyl Amides. *J. Am. Chem. Soc.* **2018**, *140* (51), 17878-17883; (j) Zhao, X.; Tu, H.-Y.; Guo, L.; Zhu, S.; Qing, F.-L.; Chu, L., Intermolecular selective carboacylation of alkenes via nickel-catalyzed reductive radical relay. *Nat. Commun.* **2018**, *9* (1), 3488; (k) Guo, L.; Tu, H.-Y.; Zhu, S.; Chu, L., Selective, Intermolecular Alkylarylation of Alkenes via Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2019**, *21* (12), 4771-4776; (l) García-Domínguez, A.; Mondal, R.; Nevado, C., Dual Photoredox/Nickel-Catalyzed Three-Component Carbofunctionalization of Alkenes. *Angew. Chem. Int. Ed.* **2019**, *58* (35), 12286-12290; (m) Shu, W.; Garcia-Dominguez, A.; Quiros, M. T.; Mondal, R.; Cardenas, D. J.; Nevado, C., Ni-Catalyzed Reductive Dicarbofunctionalization of Nonactivated Alkenes: Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2019**, *141* (35), 13812-13821.

9. For recent examples on Ni-catalyzed two-component dicarbofunctionalizations of unactivated alkenes, see: (a) Kuang, Y.; Wang, X.; Anthony, D.; Diao, T., Ni-catalyzed two-component reductive dicarbofunctionalization of alkenes via radical cyclization. *Chem. Commun.* **2018**, *54* (20), 2558-2561; (b) Kadam, A. A.; Metz, T. L.; Qian, Y.; Stanley, L. M., Ni-Catalyzed Three-Component Alkene Carboacylation Initiated by Amide C–N Bond Activation. *ACS Catal.* **2019**, *9* (6), 5651-5656; (c) Jin, Y.; Wang, C., Ni-catalysed reductive arylalkylation of unactivated alkenes. *Chem. Sci.* **2019**, *10* (6), 1780-1785; (d) Zheng, S.; Gutiérrez-Bonet, Á.; Molander, G. A., Merging Photoredox PCET with Ni-Catalyzed Cross-Coupling: Cascade Amidoarylation of Unactivated Olefins. *Chem* **2019**, *5* (2), 339-352; (e) Law, C.; Meng, Y.; Koo, S. M.; Morken, J. P., Catalytic Conjunctive Coupling of Carboxylic Acid Derivatives with 9-BBN-Derived Ate Complexes. *Angew. Chem. Int. Ed.* **2019**, *58* (20), 6654-6658; (f) Lin, Q.; Diao, T., Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019**, *141* (44), 17937-17948; (g) Huang, D.; Olivieri, D.; Sun, Y.; Zhang, P.; Newhouse, T. R., Nickel-Catalyzed Difunctionalization of Unactivated Alkenes Initiated by Unstabilized Enolates. *J. Am. Chem. Soc.* **2019**, *141* (41), 16249-16254.

10. (a) Müller, K.; Faeh, C.; Diederich, F., Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317* (5846), 1881-1886; (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V., Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37* (2), 320-330.

11. Studer, A., A "Renaissance" in Radical Trifluoromethylation. *Angew. Chem. Int. Ed.* **2012**, *51* (36), 8950-8958.

12. Anka-Lufford, L. L.; Huihui, K. M. M.; Gower, N. J.; Ackerman, L. K. G.; Weix, D. J., Nickel-Catalyzed Cross-Electrophile Coupling with Organic Reductants in Non-Amide Solvents. *Chem. Eur. J.* **2016**, *22* (33), 11564-11567.

13. Other tertiary alkyl iodides led to low yields, while primary alkyl iodides didn't react under the standard conditions.

14. Kleman, P.; González-Liste, P. J.; García-Garrido, S. E.; Cadierno, V.; Pizzano, A., Highly Enantioselective Hydrogenation of 1-Alkylvinyl Benzoates: A Simple, Nonenzymatic Access to Chiral 2-Alkanols. *Chem. Eur. J.* **2013**, *19* (48), 16209-16212.

15. Boz, E.; Nemeth, A. J.; Ghiviriga, I.; Jeon, K.; Alamo, R. G.; Wagener, K. B., Precision Ethylene/Vinyl Chloride Polymers via Condensation Polymerization. *Macromolecules* **2007**, *40* (18), 6545-6551.
16. (a) Han, Y.-C.; Zhang, Y.-D.; Jia, Q.; Cui, J.; Zhang, C., Hypervalent-Iodine-Mediated Ring-Contraction Monofluorination Affording Monofluorinated Five-Membered Ring-Fused Oxazolines. *Org. Lett.* **2017**, *19* (19), 5300-5303; (b) Raghavan S; L., R. C., Stereoselective carbon–carbon bond formation via 1,2-asymmetric induction by a β-substituent in the reaction of α-chloro sulfides with organozinc reagents. *Indian J. Chem. Sec B* **2018**, *57B*, 327-339.
17. Several byproducts including the hydroperfluoroalkylated and iodoperfluoroalkylated alkane as well as C4F9-alkenes were detected in the reaction.
18. (a) Everson, D. A.; Shrestha, R.; Weix, D. J., Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010**, *132* (3), 920-921; (b) Liang, Y.; Fu, G. C., Stereoconvergent Negishi Arylations of Racemic Secondary Alkyl Electrophiles: Differentiating between a CF3 and an Alkyl Group. *J. Am. Chem. Soc.* **2015**, *137* (30), 9523-9526.
19. Huang, L.; Zhu, C.; Yi, L.; Yue, H.; Kancherla, R.; Rueping, M., Cascade Cross-Coupling of Dienes: Photoredox and Nickel Dual Catalysis. *Angew. Chem. Int. Ed.* **2020**, *59* (1), 457-464.
20. Helmecke, L.; Spittler, M.; Baumgarten, K.; Czekelius, C., Metal-Free Activation of C–I Bonds and Perfluoroalkylation of Alkenes with Visible Light Using Phosphine Catalysts. *Org. Lett.* **2019**, *21* (19), 7823-7827.
21. Shevick, S. L.; Obradors, C.; Shenvi, R. A., Mechanistic Interrogation of Co/Ni-Dual Catalyzed Hydroarylation. *J. Am. Chem. Soc.* **2018**, *140* (38), 12056-12068.
22. Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C., Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137* (15), 4896-4899.
23. (a) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A., Ligand Redox Effects in the Synthesis, Electronic Structure, and Reactivity of an Alkyl–Alkyl Cross-Coupling Catalyst. *J. Am. Chem. Soc.* **2006**, *128* (40), 13175-13183; (b) Lin, X.; Phillips, D. L., Density Functional Theory Studies of Negishi Alkyl–Alkyl Cross-Coupling Reactions Catalyzed by a Methylterpyridyl-Ni(I) Complex. *J. Org. Chem.* **2008**, *73* (10), 3680-3688; (c) Biswas, S.; Weix, D. J., Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135* (43), 16192-16197; (d) Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X., Bimetallic Oxidative Addition Involving Radical Intermediates in Nickel-Catalyzed Alkyl–Alkyl Kumada Coupling Reactions. *J. Am. Chem. Soc.* **2013**, *135* (32), 12004-12012; (e) Schley, N. D.; Fu, G. C., Nickel-Catalyzed Negishi Arylations of Propargylic Bromides: A Mechanistic Investigation. *J. Am. Chem. Soc.* **2014**, *136* (47), 16588-16593; (f) Mohadjer Beromi, M.; Nova, A.; Balcells, D.; Brasacchio, A. M.; Brudvig, G. W.; Guard, L. M.; Hazari, N.; Vinyard, D. J., Mechanistic Study of an Improved Ni Precatalyst for Suzuki–Miyaura Reactions of Aryl Sulfamates: Understanding the Role of Ni(I) Species. *J. Am. Chem. Soc.* **2017**, *139* (2), 922-936; (g) Kc, S.; Dhungana, R. K.; Shrestha, B.; Thapa, S.; Khanal, N.; Basnet, P.; Lebrun, R. W.; Giri, R., Ni-Catalyzed Regioselective Alkylarylation of Vinylarenes via C(sp3)–C(sp3)/C(sp3)–C(sp2) Bond Formation and Mechanistic Studies. *J. Am. Chem. Soc.* **2018**, *140* (31), 9801-9805; (h) Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H., Ni-Catalyzed Reductive Coupling of Electron-Rich Aryl Iodides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2018**, *140* (43), 14490-14497; (i) Yin, H.; Fu, G. C., Mechanistic Investigation of Enantioconvergent Kumada Reactions of Racemic α-Bromoketones Catalyzed by a Nickel/Bis(oxazoline) Complex. *J. Am. Chem. Soc.* **2019**, *141* (38), 15433-15440.

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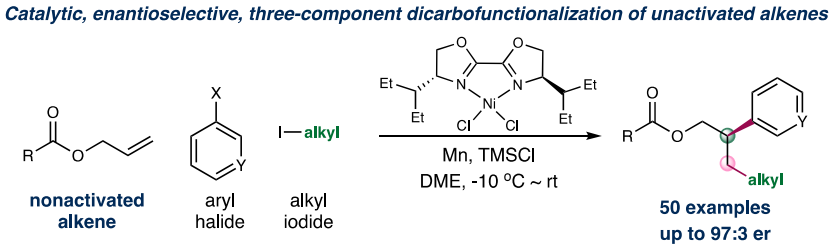
Catalytic, enantioselective, three-component dicarbofunctionalization of unactivated alkenes
nonactivated alkene
aryl halide
alkyl iodide
I—alkyl
Et
Et
Et
Et
Ni
Cl
Cl
Mn, TMSCl
DME, -10 °C ~ rt
alkyl
50 examples
up to 97:3 er