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Electron-Deficient Olefin Ligands Enable Generation of Quaternary Carbons by Ni-Catalyzed Cross-Coupling

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Supporting Information

ABSTRACT: A Ni-catalyzed Negishi cross-coupling with 1,1-disubstituted styrenyl aziridines has been developed. This method delivers valuable β-substituted phenethylamines via a challenging reductive elimination that affords a quaternary carbon. A novel electron-deficient olefin ligand, Fro-DO, proved crucial for achieving high rates and chemoselectivity for C−C bond formation over β-H elimination. This ligand is easy to access, is stable, and presents a modular framework for reaction discovery and optimization. We expect that these attributes, combined with the fact that the ligands impart distinct electronic properties to a metal, will support the invention of new transformations not previously possible using established ligands.

Transition-metal-catalyzed cross-couplings have evolved to be among the most valuable C−C and C−heteroatom bond-forming reactions in chemical synthesis.[1] Their expansive scope and mild reaction conditions are the result of numerous catalyst improvements accumulated over the years; the design of novel ligands that can tune the reactivity and selectivity of the metal center has been paramount. Identification of electron-donating ligands such as phosphines, amines, and *N*-heterocyclic carbenes represents the dominant direction in ligand development for the field thus far.[2] These ligands electronically accelerate oxidative addition and, in so doing, have enabled the discovery of previously challenging or impossible to achieve transformations (Figure A).[3] By contrast, ligands designed to electronically activate the other key parts of the cross-coupling cycle have received comparatively less attention. For example, although π-accepting, electron-deficient olefins have been shown to accelerate reductive elimination,[4] these ligands have so far only seen limited application in catalysis.[5,6] Problems associated with slow reductive elimination pervade current challenges in the field, including the development of alkyl cross-coupling reactions.[7] Thus, development of electron-deficient olefins into a modular class of ligands, in which it is possible to modify catalyst reactivity and selectivity by straightforward changes to the ligand structure, would significantly advance the field.

Since 2012, our laboratory and the groups of Michael, Minakata, and Jamison have pursued the development of methods for aziridine cross-coupling that permit the rapid synthesis of β-substituted amine products.[8,9] In particular, we discovered that an electron-deficient olefin (EDO) ligand, dimethyl fumarate (**1**), was uniquely effective in promoting nickel-catalyzed Negishi alkylations of styrenyl aziridines (Figure 1B).[8a] We subsequently found that the installation of an EDO on the *N*-protecting group of alkyl aziridines (cinsyl or Cn) successfully enabled cross-coupling with these unactivated reaction partners.[8b] Unfortunately, no conditions have yet been identified that deliver cross-coupled products with 1,1-disubstituted aziridines. In general, cross-couplings with tertiary electrophiles to generate quaternary carbons suffer from slow reductive elimination such that β-hydride elimination is a major competitive decomposition process. Nevertheless, there have been a few important breakthroughs toward solving this long-standing challenge using amine ligands and Ni catalysis.[10,11] Since EDOs are capable of accelerating reductive elimination, and the fumarate framework in particular provides a readily

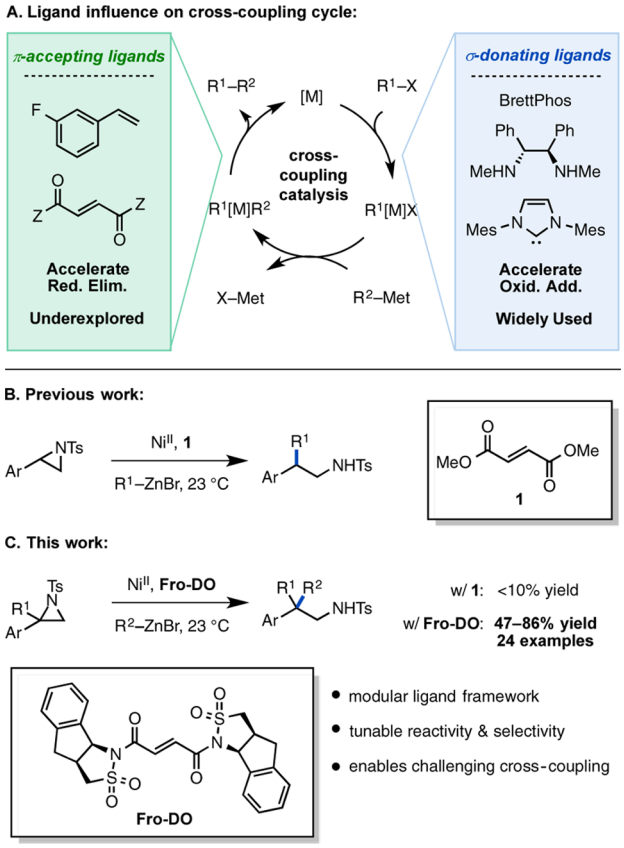

Figure 1. (A) Ligand influence on cross-coupling. (B and C) Electron-deficient olefin (EDO) ligands in aziridine cross-coupling.

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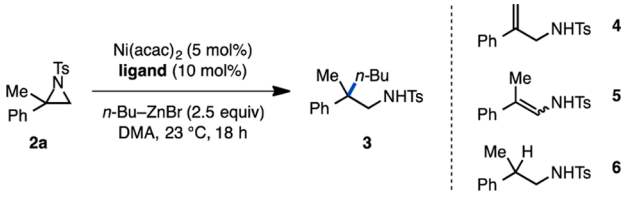
modifiable ligand platform, we wondered if a novel ligand could be devised to achieve selective cross-coupling with aziridines containing a tertiary C−N leaving group. Herein we report the successful development of a sultam-derived EDO ligand, Fro-DO, which promotes efficient cross-couplings between 1,1-disubstituted aziridines and organozinc reagents (Figure 1C).

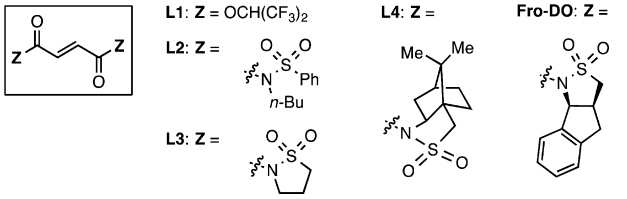
Our initial optimizations were carried out with 1-methyl-1-phenyl-*N*-tosylaziridine **2a** and *n*-BuZnBr as the nucleophile.[12] Examination of various reaction parameters using dimethyl fumarate (**1**) as the ligand provided <10% yield of the desired product **3** (Table 1, entry 2). The mass balance of the reaction

Table 1. Reaction Optimization



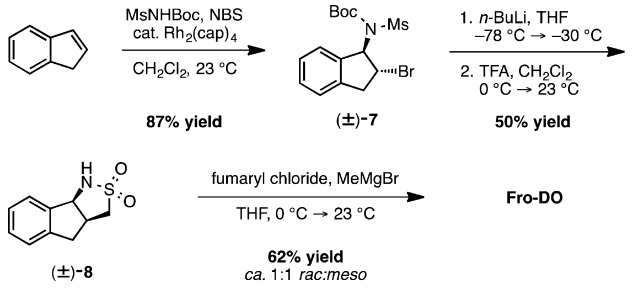
entry	ligand	yield[a]	conv.[a]
1	no ligand	<5%	45%
2	dimethyl fumarate (**1**)	8%	61%
3	maleic anhydride	<5%	54%
4	*N*-ethylmaleamide	<5%	45%
5	*m*-fluorostyrene	<5%	61%
6	*p*-benzoquinone	<5%	48%
7	**L1**	<5%	44%
8	**L2**	5%	64%
9	**L3**	9%	78%
10	**L4**	48%	73%
11	**Fro-DO**	**68%**	**89%**
12	(±)-**Fro-DO**	71%	91%
13	***meso*-Fro-DO**	68%	85%
14	10% $Ni(acac)_2$ and 20% **Fro-DO**	77%	92%

[a]Determined by GC, 0.05 mmol scale with dodecane as internal standard.



was comprised of byproducts **4**−**6** resulting from *β*-hydride elimination, as often seen in other cross-coupling protocols with tertiary electrophiles. Evaluation of other commercially available EDOs failed to improve the reaction efficiency (entries 3−6). Therefore, our focus turned to the preparation of novel EDOs based on the fumarate backbone. Ligands **L1** and **L2** bearing more *π*-deficient olefins than dimethylfumarate failed to deliver product **3** in improved yield (entries 7 and 8). However, sultam-derived fumaramide ligands **L3** and **L4** increased the reaction efficiency. Further structural modification of the sultam motif led to the discovery of ligand Fro-DO as optimal. With 5 mol % $Ni(acac)_2$ and 10 mol % Fro-DO, 1-methyl-1-phenyl-*N*-tosylaziridine **2a** underwent alkylation to provide phenethylamine **3** containing a *β*-quaternary center in 68% yield under extremely mild conditions. Notably, gram quantities of (±)-Fro-DO can be easily prepared from indene in 4 steps as a 1:1 rac/meso mixture (Scheme 1). Since use of the diastereomerically

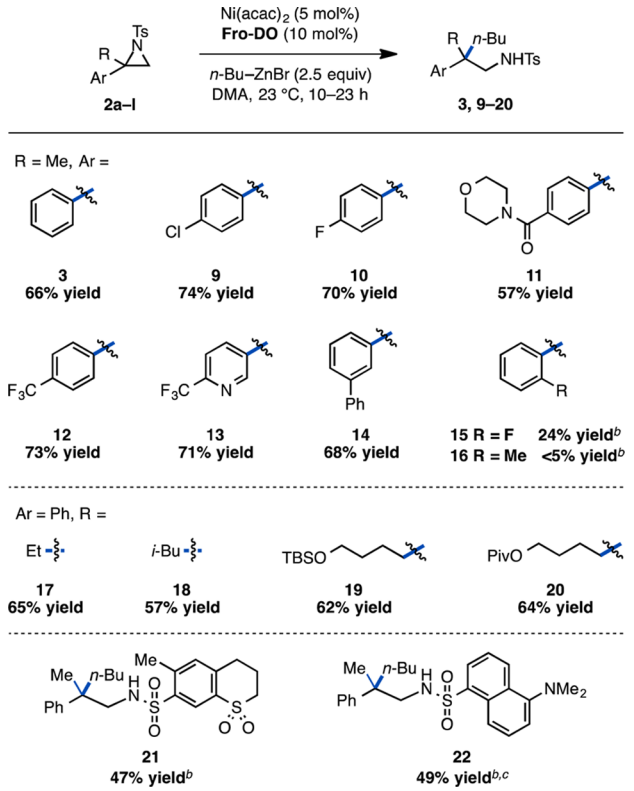
Scheme 1. Synthesis of Ligand Fro-DO



pure ligand gave similar results as the mixture (entries 11−13), the ligand was used as prepared for the following studies. Cross-coupled products arising from ring opening at the less substituted position of the aziridines were not observed in any of these cases.

With optimized conditions in hand, we investigated the scope of the aziridine coupling partner (Table 2). Whereas styrenyl

Table 2. Scope of 1,1-Disubstituted Aziridines[a]



[a]Yields are the average of two runs, 0.50 mmol scale. [b]One run. [c]0.20 mmol scale.

aziridines bearing *para*- and *meta*-substituents on the aromatic ring can be alkylated in high yield (**3**, **9**−**14**), those with *ortho*-substitution are not well-tolerated (**15** and **16**), presumably due to steric encumbrance in forming such quaternary centers. We were pleased to find that a heteroaromatic aziridine underwent coupling to afford **13** with high reaction efficiency. Furthermore, 1,1-disubstituted aziridines bearing substituents other than methyl at the benzylic position are also competent substrates (**17**−**20**). In general, sensitive functional groups such as chlorides (**9**), amides (**11**), silyl ethers (**19**), esters (**20**), sulfones (**21**), and anilines (**22**) are well-tolerated. However, 1,1-diarylaziridines fail to deliver coupled products. Finally, given the

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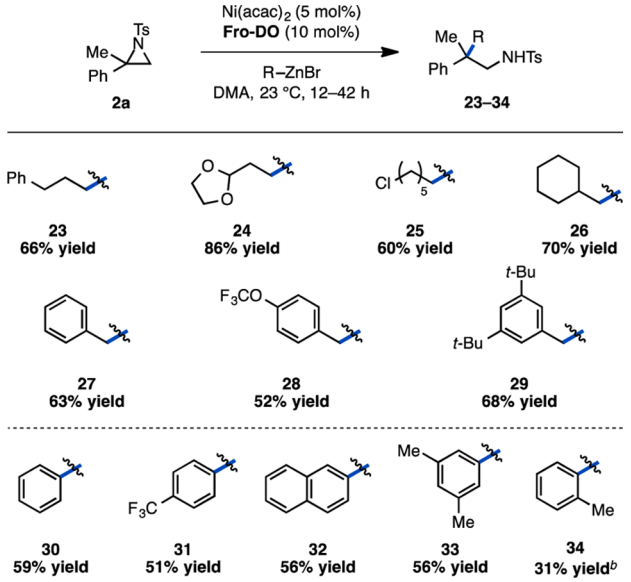
importance of sulfonamide moieties in biologically relevant molecules,[13] we decided to explore aziridines derived from the antihypertensive meticrane and the fluorescent dye dansyl amide. Gratifyingly, **21** and **22** can be obtained under standard conditions in moderate but useful yields.

The nucleophile scope was subsequently studied (Table 3). Alkyl zinc reagents bearing synthetically useful functional groups,

Table 3. Scope of Organozinc Reagents[a]

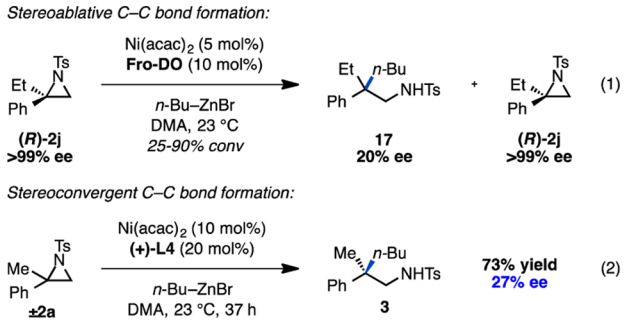


[a]Alkyl nucleophiles: RZnBr (3 equiv); Aryl nucleophiles: RZnBr (1.5 equiv), $ZnBr_2$ (1.5 equiv), DMA/THF; yields are the average of two runs, 0.50 mmol scale. [b]One run.

such as acetals (**24**), chlorides (**25**), trifluoromethoxy groups (**28**), as well as β-branching (**26**) can be used in the coupling procedure. Application of benzylzinc bromides as nucleophiles serves as a rapid route to the synthesis of β,γ-bisaryl amines from aziridines (**27**–**29**). We also found that efficient arylation can be achieved so long as 1.5 equiv of $ZnBr_2$ is included as an additive (**30**–**34**).[14] *Para*- and *meta*-substituted aryl zinc reagents are suitable reaction partners, but *ortho*-substituted aryl zinc reagents perform poorly (**34**). In addition, both electron-neutral and -poor nucleophiles can be coupled in good yield in contrast to what is possible under Friedel–Crafts conditions.[15]

Notably, the products all feature the phenethylamine motif, which comprises the core of biogenic amines.[16] Despite their low concentration in humans, these amines have been shown to play key roles in the central nervous system. Although many of their derivatives show potential as pharmaceutical agents and biomedical probes, the lack of a robust and systematic method to prepare analogs has been a hurdle for the evaluation of their activity.[17] In particular, those bearing a quaternary benzylic center have been challenging to make and their utility has rarely been explored. The current methodology provides an efficient route to these novel structures.

Our previous studies on the Ni/EDO catalyst system for Negishi couplings with monosubstituted aziridines revealed a stereoablative mechanism for C–C bond formation.[8a,b] To evaluate the stereochemical course of the present reaction, enantiopure (*R*)-**2j** was subjected to the standard reaction conditions utilizing Fro-DO as the ligand (eq 1). In accord with our previous reports, significant racemization was observed in the



formation of **17**, whereas recovered **2j** remained enantiopure. This result is consistent with an irreversible oxidative addition, at or after which a stereoablative step occurs. A likely mechanism for the oxidative addition is single-electron transfer (SET) from a reduced nickel species to generate a stabilized tertiary/benzylic radical intermediate. This mechanism presents the exciting opportunity to achieve an asymmetric variant starting from racemic aziridines. Whereas there are many robust methodologies for the racemic synthesis of aziridines, asymmetric catalytic methods for their synthesis remain quite limited.[18] Thus, a stereoconvergent cross-coupling reaction would be compelling. Unfortunately, use of (+)-Fro-DO for the coupling of (±)-**2a** with *n*-BuZnBr delivered racemic **3**. However, we were pleased to find that camphorsultam ligand (+)-**L4** delivered **3** in a promising 73% yield and 27% ee, demonstrating for the first time that an electron-deficient olefin can serve as a chiral ligand for asymmetric alkyl cross-coupling (eq 2).[6] This result also represents the first example of a stereoconvergent cross-coupling with a tertiary electrophile.

Our results raise the question: what key elements of the EDOs in Table 1 are responsible for their significant differences in reactivity? One hypothesis for why Fro-DO imparts superior efficiency to the other EDO ligands is that it features a more π-deficient olefin. However, examination of the ^{13}C NMR shifts of the olefinic carbons on these ligands reveals no correlation between the chemical shift and reaction efficiency (see Supporting Information (SI) for details).

A second hypothesis is that the sulfonamide of the ligands might bind with the Ni center and thus slow β-hydride elimination by occupying an open coordination site.[19] To gain insight into this possibility, we prepared Ni(cod)(Fro-DO) complex **35** and studied its structure by single crystal X-ray diffraction (Figure 2A). Compared with the olefinic C–C bond of the free ligand (Figure 2B), the C12–C13 bond of complex **35** shows significant elongation (1.43 vs 1.33 Å), and the C11–C12–C13–C14 torsion angle is 167.80° as opposed to 173.52° in the free ligand. These differences, along with the upfield ^1H NMR chemical shift of the olefinic protons of Fro-DO in complex **35**, all indicate strong metal-to-ligand π-back bonding. However, at least in the solid state, there is no evidence of sulfonamide coordination to Ni(0). Importantly, complex **35** is catalytically active: alkylated product **3** was obtained in 57% yield from **2a** using 5 mol % **35** and 5 mol % Fro-DO under otherwise standard conditions.

The structure of complex **35** suggests an alternative explanation for the enhanced reactivity of ligand Fro-DO. This ligand features a U-shaped conformation due to dipole minimization with Ni binding to the concave face and creates a sterically congested environment around the metal center.[20] Thus, Fro-DO may also accelerate reductive elimination by forcing the two organic groups on nickel into proximity. This

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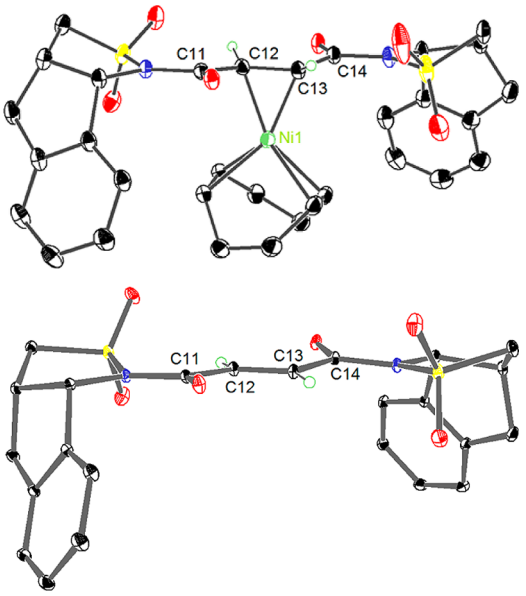

Figure 2. (A) Solid-state structure of Ni(cod)(Fro-DO) **35** at 30% probability ellipsoids. DMA solvent molecule omitted for clarity. H-atoms omitted for clarity, except for those attached to C12 and C13. (B) Solid-state structure of Fro-DO at 30% probability ellipsoids. H-atoms omitted for clarity, except for those attached to C12 and C13.

phenomenon is analogous to the manner in which sterically bulky, electron-rich phosphine and NHC ligands are thought to facilitate reductive elimination.[3,21]

In summary, we identified a novel, highly active electron-deficient olefin ligand, Fro-DO, that enables nickel-catalyzed cross-coupling with 1,1-disubstituted aziridines and organozinc reagents to generate quaternary centers under mild conditions.[22] Our studies highlight that EDOs can enable reactions not previously possible with traditional ligands for cross-coupling. Also, our studies provide a unique example that the stability, ease of synthesis, and modularity of EDOs render them an attractive ligand class for reaction optimization. The impact the structure of these ligands has on catalyst activity and chemo- and enantioselectivity offers an exciting future direction for exploring their utility in other transition-metal-catalyzed reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, details of optimization studies, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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