

Ni-Catalyzed Conversion of Enol Triflates to Alkenyl Halides

Julie L. Hofstra[†], Kelsey E. Poremba[†], Alex M. Shimozono[†], and Sarah E. Reisman^{*}

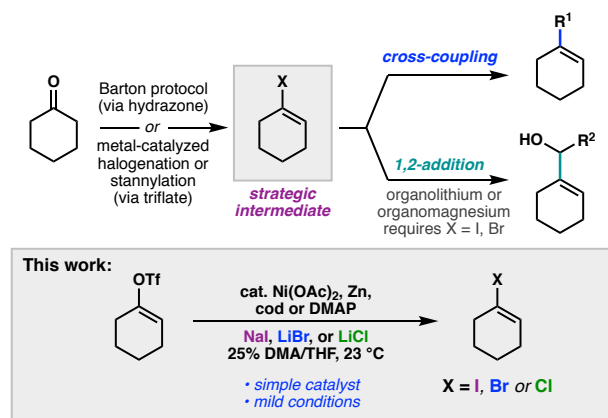
Abstract: A Ni-catalyzed halogenation of alkenyl triflates was developed that enables the synthesis of a broad range of alkenyl iodides, bromides, and chlorides under mild reaction conditions. The reaction utilizes inexpensive, bench stable Ni(OAc)₂·4H₂O as a pre-catalyst and proceeds at room temperature in the presence of sub-stoichiometric Zn and either cod or DMAP as a supporting ligand.

Alkenyl halides are versatile functional groups that can be used in a variety of carbon–carbon and carbon–heteroatom bond-forming reactions. For example, alkenyl halides are commonly used as substrates in transition metal-catalyzed cross-coupling reactions¹ or are converted via metal-halogen exchange to nucleophiles for 1,2-additions to carbonyl compounds (Scheme 1).² Furthermore, the alkenyl halide moiety appears in some natural products and bioactive molecules.³ Whereas acyclic alkenyl halides are easily prepared from the corresponding alkyne⁴ or aldehyde,⁵ most cyclic alkenyl halides are synthesized from the corresponding ketone. The most direct method is the Barton reaction (and variations thereof),^{6,7} which proceeds through an intermediate hydrazone. These reactions are notoriously capricious: the formation of the requisite hydrazone can be challenging on sterically encumbered substrates and the halogenation step often produces mixtures of alkenyl halide isomers or dihalide side products.⁸

As a result, enol triflates, which can be prepared directly from cyclic ketones under either kinetic or thermodynamic control, have emerged as attractive “pseudohalides” for transition metal-catalyzed cross-coupling processes. Unfortunately, enol triflates cannot be directly converted to the corresponding alkenyllithium or alkenylmagnesium species commonly employed in 1,2-addition reactions. In cases where the Barton procedure to prepare the alkenyl halide is poor yielding, a multistep alternative is frequently employed: 1) conversion of the ketone to enol triflate, 2) conversion of the triflate to the alkenyl stannane, and 3) conversion of the stannane to the alkenyl halide.⁹ Direct, mild methods to convert enol triflates to alkenyl halides, without proceeding through

organostannane intermediates, can streamline the preparation of these valuable synthons.

Indeed, Buchwald has reported a Pd-catalyzed reaction to convert alkenyl triflates to alkenyl bromides and chlorides;¹⁰ however, there are no examples of alkenyl iodide formation, and the reaction requires an expensive ligand, temperatures greater than 100 °C, or additives such as fluoride salts or ^tBu₃Al. These additives limit the functional group compatibility of the transformation, particularly with commonly used groups such as silyl ethers. More recently, Hayashi reported a Ru-catalyzed method to convert enol triflates to iodides, bromides, or chlorides that proceeds at ambient temperature; however, the requisite ruthenium catalyst is not commercially available and limited examples of alkenyl iodide formation are reported.¹¹



Scheme 1. Synthesis and utility of alkenyl halides.

During our investigations of Ni-catalyzed asymmetric reductive coupling reactions of alkenyl bromides,¹² we observed an off-pathway halide exchange process that generated alkenyl chlorides and iodides. Whereas Ni-catalyzed aryl¹³ and alkenyl halide exchange processes have been previously reported and extensively investigated,^{13b, 14} development of the corresponding reactions of enol triflates have been limited to a single report describing bromination of dihydropyranyl enol triflates.^{15,16a} Having observed promising reactivity with enol triflates in our investigation of asymmetric reductive coupling reactions,¹⁷ we hypothesized that an appropriate Ni catalyst and inexpensive halide salts might enable the direct conversion of alkenyl triflates to alkenyl halides under mild conditions. In this communication, we report the development of a Ni-catalyzed triflate-halide exchange (triflex) reaction, which provides access to alkenyl iodides, bromides, and chlorides in good to excellent yields (Scheme 1).

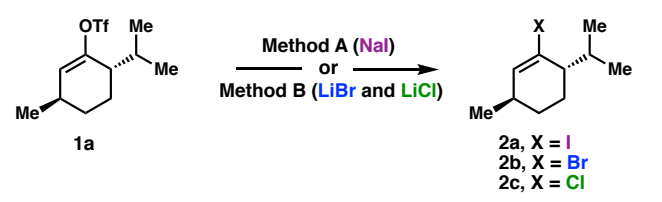
[*] J. L. Hofstra^[†], K. E. Poremba^[†], A. M. Shimozono^[†], and Prof. S. E. Reisman
The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology
Pasadena, CA 91125 (USA)
Email: reisman@caltech.edu
Homepage: <http://reismangroup.caltech.edu>

[†] These authors contributed equally to this research and are listed alphabetically.

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Our reaction development began with enol triflate **1a**, prepared in one step from menthone, with the goal of identifying general conditions that could provide the alkenyl iodide, bromide, or chloride simply by changing the halide salt. Initial optimization efforts using Ni(cod)₂ as a catalyst revealed that a mixed DMA/THF solvent system and short reaction times were optimal, and that bidentate ligands (phosphine, amine, and pyridine) inhibited the reaction.¹⁸ Informed by these results, we screened a variety of Ni(II) pre-catalysts in combination with Zn⁰ and cod and ultimately found that Ni(OAc)₂•4H₂O afforded promising results across all three reactions.¹⁸ While 5 mol % Ni(OAc)₂•4H₂O and longer reaction times appeared general for the bromination and chlorination reactions, the iodination required DMAP as a supporting ligand in order to obtain complete conversion (Table 1, entries 1 and 13).¹⁹ Moreover, although comparably high yields were obtained with various Ni loadings when **1a** was used (Table 1, entries 1, 9, and 10), higher Ni loading (10 mol %) and shorter reaction time (6 h) was deemed optimal in order to maximize conversion while minimizing protodetriflation across a variety of substrates.²⁰

Table 1. Optimization of reaction conditions.^[a]



Entry	Deviation from Standard Conditions	Yield 2a (%) ^[b]	Yield 2b (%) ^[b]	Yield 2c (%) ^[b]
1	None	87	79	75
2	Ni(acac) ₂	14	83	82
3	Ni(X) ₂	75	82	0
4	Ni(cod) ₂	70	81	83
5	DMA	12	0	0
6	THF	82	69	40
7	DMF	0	18	0
8	MeCN	24	33	8
9	½ x Ni(OAc) ₂ •4H ₂ O loading	90	84	81
10	2 x Ni(OAc) ₂ •4H ₂ O loading	87	77	77
13	-DMAP (I) / + DMAP (Br/Cl)	33	94	91

[a] **Method A:** Ni(OAc)₂•4H₂O (10 mol %), Zn (20 mol %), cod (20 mol %), DMAP (20 mol %), NaI (1.5 equiv), 25% DMA/THF (0.25M), 23 °C, 6 h. **Method B:** Ni(OAc)₂•4H₂O (5 mol %), Zn (10 mol %), cod (10 mol %), LiBr or LiCl (1.5 equiv), 25% DMA/THF (0.25M), 23 °C, 16 h. Reactions conducted under inert atmosphere on 0.1 mmol scale. [b] Determined by ¹H NMR versus 1,2,4,5-tetrachloronitrobenzene as an internal standard.

Having identified satisfactory reaction conditions, the substrate scope of the Ni-catalyzed halogenation reaction was investigated (Table 2). The halide exchange was found to be

compatible with a variety of common functional groups, including amines (**4**), carbamates (**5**, **13**), pyridines (**20**), alkenes (**10**, **12**), esters (**19**), ketals (**6**, **14**), and enones (**11**). Dienyl halides could also be prepared in good yields, although the dienyl iodides **10** and **14** required longer reaction times and excess NaI in order to achieve high conversion. Chemoselective halogenation of the alkenyl triflate was observed in preference to aryl triflates (**15**, **20**), aryl chlorides (**9**, **21**), and aryl boronates (**22**); however, competitive halide exchange was observed in the presence of aryl bromides and iodides.¹⁸

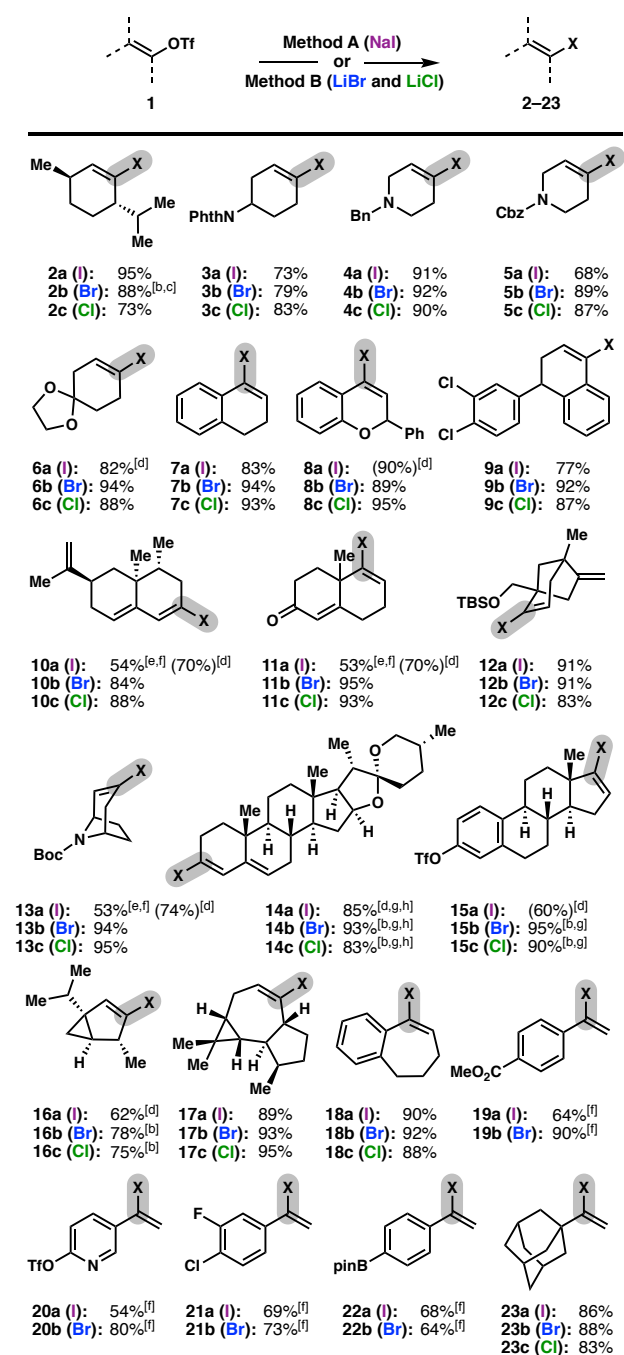
Although the Ni-catalyzed halogenation exhibits good functional group tolerance, the iodination, bromination, and chlorination did not perform equally well. In particular, the initial iodination conditions proved general for roughly half the substrates. In cases where the iodination was sluggish (**6**, **8**, **10**, **11**, **13-16**), longer reaction times and increased concentrations of NaI improved conversions; however, the improved reactivity was often accompanied by increased amounts of reduction,²⁰ and the alkene could be difficult to separate from the alkenyl iodides (**8a**, **10a**, **11a**, **13a**, **15a**). Thus, for a subset of these substrates (**10**, **11**, **13**), use of Ni(cod)₂ in conjunction with the enol nonaflate afforded access to the alkenyl iodides, which could be isolated without detectable quantities of corresponding alkene.^{16b}

In contrast, the bromination and chlorination reactions were generally more efficient and robust. For most substrates, complete conversions were achieved with lower Ni loading and without the need for DMAP, although DMAP provided improved yields in cases where incomplete conversion was observed with cod (**14-16**). In addition, for 1-arylvinylyl triflates (**19-22**, Table 2) the use of Ni(cod)₂ (method C) provided cleaner reaction profiles for the bromination and iodination.²¹

To better understand the Ni-catalyzed halogenation of enol triflates, and the iodination in particular, a series of mechanistic experiments were performed. Ni(cod)₂ was used for these studies, since the reactions were homogeneous. The iodination of **1a** exhibits an induction period at low Ni(cod)₂ loadings (e.g. 0.5 mol %, 1 mol %) (Scheme 2a).²² Plotting V_{max} vs. [Ni] revealed that the reaction has a positive-order dependence on [Ni] that negatively deviates from first order at higher [Ni], suggesting the formation of dimeric (or higher order) off-cycle species at higher [Ni].²³ No change in the rate of iodination of **1a** is observed when the amount of NaI is increased beyond 1 equiv.

A crossover experiment was designed to evaluate the reversibility of alkenyl halide formation: treatment of a 1:1 mixture of **24-OTf** and **25-Br** with Ni(cod)₂ (10 mol %) in 1:3 DMA/THF at 23 °C resulted in complete recovery of **24-OTf** and **25-Br**, without detection of crossover products **25-OTf** or **24-Br** (Scheme 2b). Addition of 0.1 or 1.0 equiv LiBr resulted in conversion of **24-OTf** to **24-Br** in 10% and 90% yield, respectively;^{24,25} no **25-OTf** was detected at any point in either reaction. Monitoring the reaction by ¹H NMR confirms that no oxidative addition of **24-OTf** occurs in the absence of halide salt. Subjection of alkenyl iodide **25-I** to Ni(cod)₂ (10 mol %) and metal triflate salts (e.g. NaOTf) did not result in enol triflate

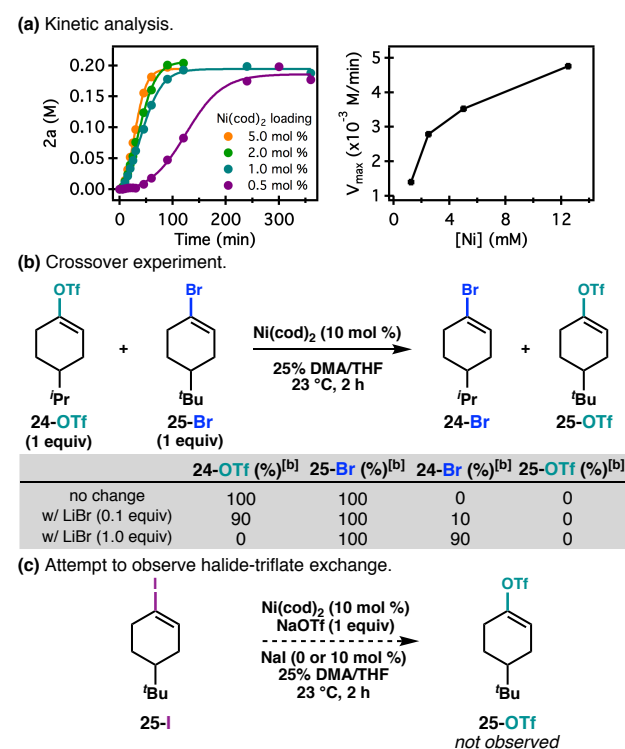
Table 2. Scope of alkenyl halides.^[a]



[a] Reactions conducted under inert atmosphere on 0.3 mmol scale. Isolated yields (¹H NMR yield determined with internal standard). **Method A:** Ni(OAc)₂•4H₂O (10 mol %), Zn (20 mol %), cod (20 mol %), DMAP (20 mol %), NaI (1.5 equiv), 25% DMA/THF (0.25M), 23 °C, 6 h. **Method B:** Ni(OAc)₂•4H₂O (5 mol %), Zn (10 mol %), cod (10 mol %), LiBr or LiCl (1.5 equiv), 25% DMA/THF (0.25M), 23 °C, 16 h. [b] DMAP (10 mol %) instead of cod. [c] 5 mmol scale. [d] 5 equiv NaI was used in the absence of cod, 36 h reaction time. [e] Enol nonaflate used. [f] **Method C:** Ni(cod)₂ (10 mol %), MX (1.5 equiv), 25% DMA/THF (0.25M), 23 °C, 16 h. [g] 0.2 mmol scale. [h] Conducted at 0.125 M.

formation (Scheme 2c).²⁶ Taken together, these results suggest that oxidative addition of the alkenyl triflate is irreversible, or that halide exchange for triflate in the oxidative addition complex is rapid and irreversible. In either scenario, the fact that the enol triflate is irreversibly consumed enables the reaction to proceed in good yield to the respective alkenyl halides. This is in contrast to Ni-catalyzed halide exchange reactions, which are thermodynamically driven equilibrium processes.^{13b} For example, after 2 h, an 85:15 mixture of **25-Br**:**25-I** is obtained for both the Ni-catalyzed reactions of **25-Br** with LiI, or **25-I** with LiBr.¹⁸

Scheme 2. Mechanistic investigation.^[a]



[a] Reactions conducted under inert atmosphere on 0.2 mmol scale. [b] Determined by GC analysis versus undecane as an internal standard.

In conclusion, a mild Ni-catalyzed halogenation of alkenyl triflates has been developed. By modifying the halide salt, alkenyl iodides, bromides, or chlorides can be obtained using a simple, inexpensive catalyst system. These reactions proceed at room temperature, afford the alkenyl halides in good to excellent yields, and exhibit good functional group tolerance.

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Keywords: nickel • halogenation • enol triflates • catalysis • alkenyl halides

- ¹ (a) *Metal-catalyzed Cross-Coupling Reactions*; De Meijer, A., Diederich, F., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: 2004; Vols. 1 & 2. (b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
- ² M. Schlosser, Ed.; John Wiley & Sons, Inc.: 2013.
- ³ (a) G. W. Gribble, Springer-Verlag: Wien, Austria, 1996. (b) G. W. Gribble, Springer-Verlag: Wien, Austria, 2010. (c) G. W. Gribble, *Mar. Drugs*. **2015**, *13*, 4004.
- ⁴ (a) D. W. Hart, T. F. Blackburn, J. Schwartz, *J. Am. Chem. Soc.* **1975**, *97*, 679. (b) H. C. Brown, C. Subrahmanyam, T. Hamaoka, N. Ravindran, D. H. Bowman, S. Misumi, M. K. Unni, V. Smayaji, N. G. Bhat, *J. Org. Chem.* **1989**, *54*, 6068. (c) F. Gao, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10961. (d) M. R. Uehling, R. P. Rucker, G. Lalic, *J. Am. Chem. Soc.* **2014**, *136*, 8799. (e) J. Derosa, A. L. Cantu, M. N. Boulous, M. L. O'Duill, J. L. Turnbull, Z. Liu, D. M. De La Torre, K. M. Engle, *J. Am. Chem. Soc.* **2017**, *139*, 5183.
- ⁵ (a) K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 2173.
- ⁶ (a) D. H. R. Barton, R. E. O'Brien, S. Sternhell, *J. Chem. Soc.* **1962**, 470. Modified Barton procedure: (b) M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc.* **2004**, *126*, 5436. (c) D. P. Ojha, K. R. Prabhu, *Org. Lett.* **2015**, *17*, 18. (d) A. Spaggiari, D. Vaccari, P. Davoli, G. Torre, F. Prati, *J. Org. Chem.* **2007**, *72*, 2216.
- ⁷ The trisilylhydrazones can be converted directly to the corresponding alkenyllithium reagents. (a) J. E. Stemke, A. R. Chamberlin, F. T. Bond, *Tetrahedron Lett.* **1976**, *34*, 2947. (b) A. R. Chamberlin, J. E. Stemke, F. T. Bond, *J. Org. Chem.* **1978**, *43*, 147. For a review, see: (c) R. M. Adlington, A. G. M. Barrett, *Acc. Chem. Res.* **1983**, *16*, 55.
- ⁸ For a discussion of the challenges associated with hydrazone synthesis, see ref 5b, and references found therein.
- ⁹ For a recent example of this sequence in total synthesis, see: A. D. Hutters, K. W. Quasdorf, E. D. Styduhar, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 15797.
- ¹⁰ (a) X. Shen, A. M. Hyde, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14076. (b) J. Pan, X. Wang, Y. Zhang, S. L. Buchwald, *Org. Lett.* **2011**, *13*, 4974.
- ¹¹ (a) E. Shirakawa, Y. Imazaki, T. Hayashi, *Chem. Commun.* **2009**, 5088. (b) E. Imazaki, E. Shirakawa, R. Ueno, T. Hayashi, *J. Am. Chem. Soc.* **2012**, *134*, 14760.
- ¹² (a) A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2014**, *136*, 14365. (b) N. Suzuki, J. L. Hofstra, K. E. Poremba, S. E. Reisman, *Org. Lett.* **2017**, *19*, 2150.
- ¹³ (a) K. Takagi, N. Hayama, T. Okamoto, *Chem. Lett.* **1978**, 191. (b) T. T. Tsou, J. K. Kochi, *J. Org. Chem.* **1980**, *45*, 1930.
- ¹⁴ (a) K. Takagi, N. Hayama, S. Inokawa, *Chem. Lett.* **1978**, 1435. (b) M. C. J. M. Hooijdonk, T. H. A. Peters, S. F. Vasilevsky, L. Brandsma, *Syn. Commun.* **1994**, *24*, 1261. For reviews, see: (c) D. A. Petrone, J. Ye, M. Lautens, *Chem. Rev.* **2016**, *116*, 8003. (d) G. Evano, A. Nitelet, P. Thilmann, D. F. Dewez, *Front. Chem.* **2018**, 6:114.
- ¹⁵ (a) J. E. Milne, K. Jarowicki, P. J. Kocienski, *Synlett*, **2002**, *4*, 607. (b) The authors note that chlorination and iodination is also feasible, but no yields are reported. Application of these conditions to substrate **1a** provided products **2a**, **2b**, and **2c** in <10% yield. See the Supporting Information.
- ¹⁶ (a) A Ni-catalyzed trifluoromethylthiolation of alkenyl triflates was recently reported: A. Dürr, G. Yin, I. Kalvet, F. Napoly, F. Schoenebeck, *Chem. Sci.* **2016**, *7*, 1076. (b) Use of an enol nonaflate in place of the enol triflate improved the yield for one example in the above report.
- ¹⁷ J. L. Hofstra, A. H. Cherney, C. M. Ordner, S. E. Reisman, *J. Am. Chem. Soc.* **2018**, *140*, 139.
- ¹⁸ See Supporting Information.
- ¹⁹ The precise role of DMAP remains unclear. (a) *Org. Lett.* **2017**, *19*, 2118. (b) *J. Org. Chem.* **2018**, *83*, 14036.
- ²⁰ Protodetriflation was observed in up to equimolar amounts with respect to Ni loading; the amount of protodetriflation observed was also dependent on substrate and reaction time.
- ²¹ The treatment of 1-arylviny triflates with LiCl results in a competitive, non-Ni-mediated elimination to afford the aryl acetylenes. Yang, D. Wu, Z. Lu, H. Sun, A. Li, *Org. Biomol. Chem.* **2016**, *14*, 5591–5594.
- ²² Addition of exogenous cod inhibits the rate of the reaction, indicating that ligand dissociation could be the source of the induction period.
- ²³ D. G. Blackmond, *J. Am. Chem. Soc.* **2015**, *137*, 10852.
- ²⁴ No evidence of oxidative addition is observed when enol triflate **1a** and Ni(cod)₂ (5 mol %) were mixed in the presence or absence of NaOTf. However, upon addition of a metal halide salt, conversion of **1a** to the alkenyl halide (**2a-c**) was observed concomitantly with the formation of a Ni(I)-X species. The same Ni(I)-X species were detected upon mixing **2a-c** and Ni(cod)₂ (5 mol %). Oxidative addition of aryl triflates to (dppf)Ni(cod) was previously shown to form Ni(I) complexes: S. Bajo, G. Laidlaw, A. R. Kennedy, S. Sproules, D. J. Nelson, *Organomet.* **2017**, *36*, 1662–1672. (b) I. Kalvet, Q. Guo, G. J. Tizzard, F. Schoenebeck, *ACS Catal.* **2017**, *7*, 2126.
- ²⁵ Relevant mechanistic studies: M. M. Beromi, A. Nova, D. Balcells, A. M. Brasacchio, G. W. Brudvig, L. M. Guard, N. Hazari, D. J. Vinyard, *J. Am. Chem. Soc.* **2017**, *139*, 922.
- ²⁶ The reaction was sampled every 5 minutes, but at no time was enol triflate **25-OTf** detected.
