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Enantioselective Alkynylation of Trifluoromethyl Ketones Catalyzed by Cation-Binding Salen Nickel Complexes.

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Abstract: Cation-binding salen nickel catalysts were developed for the enantioselective alkynylation of trifluoromethyl ketones in high yield (up to 99%) and high enantioselectivity (up to 97% ee). The reaction proceeds with substoichiometric quantities of base (10-20 mol% KO*t*-Bu) and open to air. In the case of trifluoromethyl vinyl ketones, excellent chemo-selectivity was observed, generating 1,2-addition products exclusively over 1,4-addition products. UV-vis analysis revealed the pendant oligo-ether group of the catalyst strongly binds to the potassium cation (K^+) with 1:1 binding stoichiometry (K_a = 6.6 × 10^5 M^{-1}).

Fluorinated organic compounds have proven to be exceptionally useful in many areas of organic chemistry, including materials, agrochemicals, and pharmaceuticals.[1] In particular, chiral trifluoromethyl substituted tertiary alcohols and related derivatives are important structural motifs present in a number of bioactive compounds.[2] Of particular importance is Efavirenz, a frequently prescribed HIV reverse transcriptase inhibitor (Figure 1a).[3] One attractive strategy for the synthesis of such stereocenters is the asymmetric alkynylation of trifluoromethyl ketones, as this type of reaction may be catalytic in base, resulting in exceptionally mild reaction conditions. Furthermore, the newly installed alkyne functional handle may be easily converted to a diverse array of functional groups.

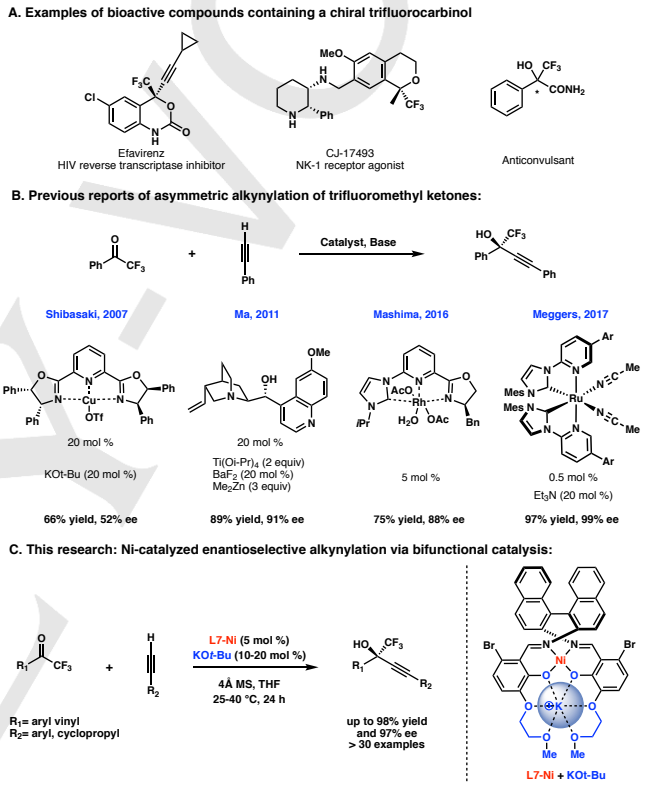

Figure 1. Enantioselective addition of terminal alkynes to trifluoromethyl ketones.

Since Carreira's pioneering report,[4a] several catalysts have been developed for the enantioselective alkynylation of aldehydes,[4] imines,[5] and alkyl ketones.[6] In contrast, there are fewer reports on the enantioselective alkynylation of trifluoromethyl ketones,[7,8] as the high reactivity of these electron-deficient electrophiles has led to significant challenges associated with facial selectivity. Although there have been some reports on the enantioselective variant of this transformation, they all suffer from significant drawbacks, such as high temperatures,[7a] large excesses of expensive reagents,[7b,d] or the use of precious, second-row transition metals as catalysts (Figure 1b).[7c,h-k]

In an effort to develop a more sustainable method for the enantioselective alkynylation of trifluoromethyl ketones, we turned our attention to the development of a cooperative catalyst involving a Lewis acid and Brønsted base (Figure 1c).[9] The use of a single catalytic species to activate and bring together both the nucleophile and electrophile could lead to a well-defined environment for the reactive intermediates, which could enable

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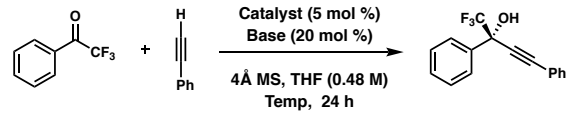
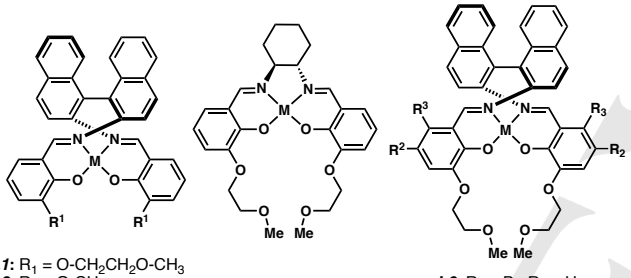
Table 1. Optimization of Reaction Conditions[a]



1a 1 equiv + *2a* 4 equiv → *3aa*

Entry	Metal	Ligand	Base	Temp (°C)	Yield (%)[b]	% ee[c]
1	Ni	***L1***	KO*t*-Bu	50	97	84
2	Ni	***L2***	KO*t*-Bu	50	48	82
3	Ni	***L3***	KO*t*-Bu	50	86	86
4	Ni	***L4***	KO*t*-Bu	50	–	–
5	Co	***L1***	KO*t*-Bu	50	91	49
6	Zn	***L1***	KO*t*-Bu	50	64	77
7	Pd	***L1***	KO*t*-Bu	50	–	–
8	Ni	***L1***	LiO*t*-Bu	50	86	78
9	Ni	***L1***	NaO*t*-Bu	50	83	85
10	Ni	***L1***	KO*t*-Bu	25	93	89
11	Ni	***L1***	KO*t*-Bu	–10	–	–
12	Ni	***L5***	KO*t*-Bu	50	–	–
13	Ni	***L6***	KO*t*-Bu	50	97	88
14	Ni	***L7***	KO*t*-Bu	50	95	91
15	Ni	***L7***	KO*t*-Bu	25	93	93



L1: R_1 = O-CH_2CH_2O-CH_3
L2: R_1 = O-CH_3
L3: R_1 = O-[CH_2CH_2O]$_2$-CH_3
L4: R_1 = *t*-Bu

L5

L6: R_2 = Br, R_3 = H
L7: R_2 = H, R_3 = Br

[a]Reactions were performed on a 0.242 mmol scale. See Supporting Information for catalyst synthesis. [b]Isolated yields. [c]The ee values were determined by HPLC analysis.

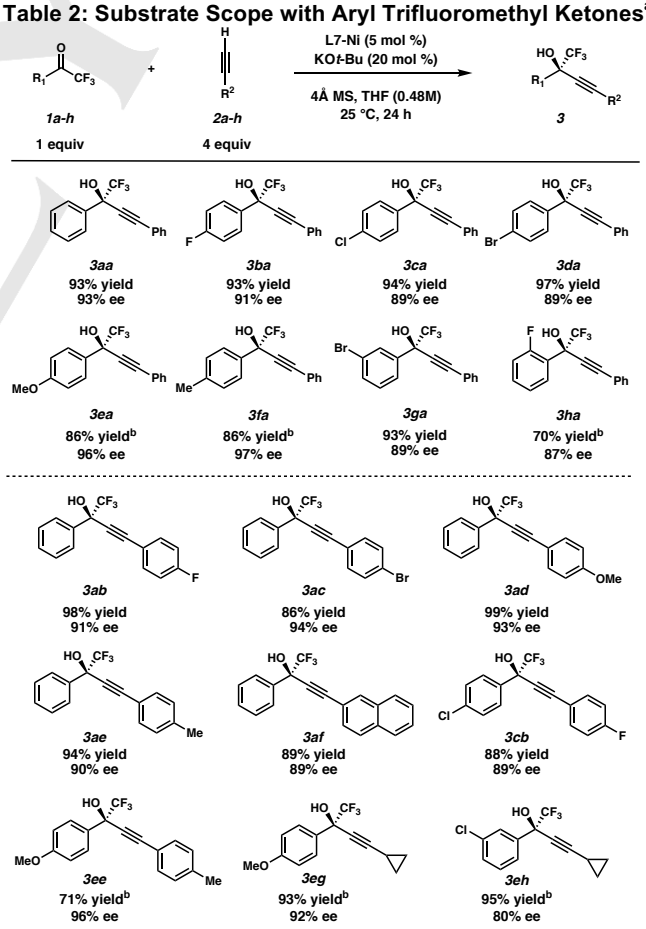
efficient control over the facial selectivity.[10] We envisioned that the use of the salen ligand framework with a pendant crown ether[11,12] which can interact with an alkali metal cation would facilitate this form of cooperative catalysis, as the Lewis acid and Brønsted base could be held in close proximity by a very rigid and specific structure.

To assess the efficacy of this type of cooperative catalyst we first synthesized and tested a number of ligand frameworks possessing oligo-ethers of varying length. We were pleased to find that ligand **L1,** with a binapthyl backbone and methoxyethane side chains, in combination with a Ni Lewis Acid and KO*t*-Bu Brønsted Base, furnished the desired product in excellent yields and ee (Table 1, entry 1). Interestingly, we found that although oligo-ether chain length did not have a significant effect on the ee, it did have an effect on the yield. Switching to a ligand possessing methoxy substituents (**L2**), or extending the chain length (**L3**) resulted in less efficient catalysts (entries 2 and 3). It is also important to note that the presence of a coordinating ether moiety was critical for reactivity, as a *tert*-butyl substituent at this position completely shut down the reaction (entry 4, **L4**). We found Ni(II) to be the optimal Lewis Acid; switching to Co or Zn led to a significant drop in ee, and Pd led to complete loss of reactivity (entries 5-7).

Next, we assessed the importance of the counter-ion on the *tert*-butoxide base. The highest enantioselectivity and yield was observed with KO*t*-Bu; both LiO*t*-Bu and NaO*t*-Bu led to a slight reduction in yield and ee (entry 1 vs entries 8 and 9). When the reaction temperature was lowered from 50 °C to 25 °C, the ee was increased to 89% ee (entry 10). Lowering the temperature even further to –10 °C, however, led to the complete loss of reactivity (entry 11).

Having investigated all other parameters, we returned to our ligand, focusing on examining the effect of different steric and electronic modifications on the backbone. We found that the binapthyl backbone was crucial for reactivity: when a ligand possessing a cyclohexyl backbone was used instead, no product was observed (entry 12). In agreement with the work of Wang and co-workers[13] we found that the introduction of bromide substituents on the salicyl arenes led to a slight improvement in the ee (entries 13 and 14). Using the 6-Bromo-Salen ligand (**L7**), the product was obtained in 93% yield and 93% ee at 25 °C under air (entry 15).

Table 2: Substrate Scope with Aryl Trifluoromethyl Ketones[a]



(a) Isolated yields on 0.242 mmol scale. Enantiomeric excess was determined by HPLC analysis. (b) Isolated yield after 48 h.

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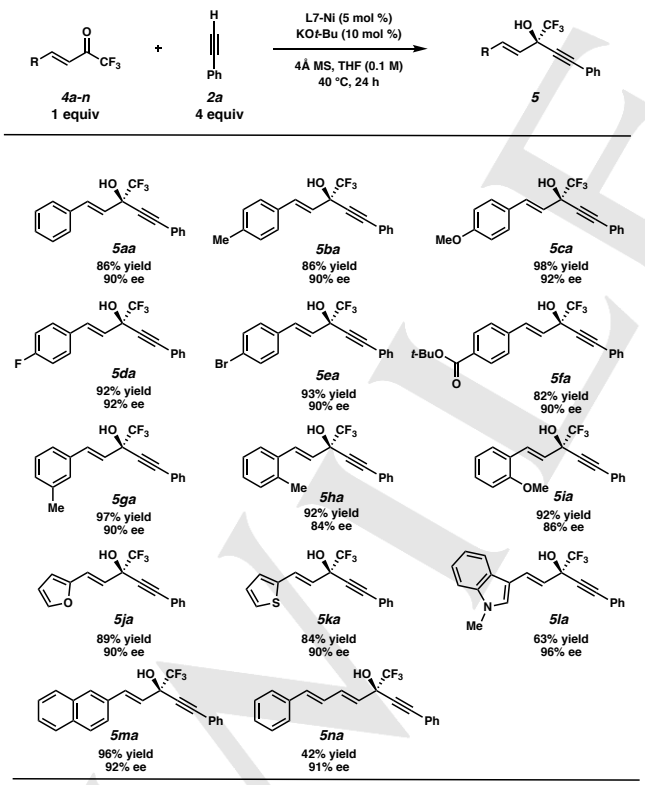
With the optimized reaction conditions in hand, we explored the substrate scope of the asymmetric alkynylation (Table 2). We found that electrophiles possessing both electron-donating substituents (**3aa**, **3ea**, **3fa**) and electron-withdrawing substituents (**3ba**, **3ca**, **3da**) at the *para*-position of the arene were well-tolerated, resulting in the desired products in up to a 97% ee and 97% yield. Although substitution at the *meta*-position of the aryl ring was also tolerated (**3ga**), *ortho*-substitution did lead to a drop in reactivity (**3ha**). We noted that generally, the yields for electron-deficient trifluoromethylketones were slightly higher than with electron-rich substrates, with the latter requiring extended reaction times. However, we did note that the ee's for electron-rich substrates were consistently higher than their electron-deficient counter-parts.

We found that the nature of the alkyne had a less pronounced effect on the overall outcome of the reaction, and alkynes possessing both electron-withdrawing (**3ab**, **3ac**, **3cb**) and electron-donating substituents (**3ad**, **3ae**, **3ee**) at the *para*-position of the aryl substituent were well-tolerated. Furthermore, we were pleased to see that a bulky napthyl substituent (**3af**) and a cyclopropyl substituent (**3eg** and **3eh**) also led to product formation in good yields and ee.

Table 3. Substrate scope with Trifluoromethyl Vinyl Ketones[a]



(a) Isolated yields on 0.2 mmol scale. enantiomeric excess was determined by SFC analysis.

Gratifyingly, we found that vinyl trifluoromethyl ketones were also tolerated under slightly modified reaction conditions (See Supporting Information for more details). Substrates possessing aryl rings with substituents at the *para* (**5ba**, **5ca**, **5da**, **5ea**), *meta* (**5ga**), and even *ortho* (**5ha** and **5ia**) positions were all well-tolerated. We were also pleased to see that a *tert*-butyl ester-containing substrate (**5fa**) and a diene (**5na**) fared well under these mild reaction conditions. Even substrates possessing heteroaromatic substituents such as a furan (**5aj**), thiophene (**5ak**), and indole (**5al**) led to product formation in excellent ee.

To investigate the binding behavior between **L7-Ni** and K^+, we carried out metal ion titration studies by UV-vis absorption spectroscopy.[14] Upon addition of KO*t*-Bu to a solution of **L7-Ni**, the UV-vis absorption spectra exhibited characteristic peaks at 350, 403, and 350 nm with two clear isosbestic points at 376 and 460 nm, as shown in **Figure 4a**. The absorbance at 403 nm for **L7-Ni**/K^+ tended to proportionally increase with KO*t*-Bu concentration up to 20 μM, and then reached saturation region. Job plot analysis (**Figure 4b**) was in good agreement with the titration study, clearly confirming that **L7-Ni** binds to K+ through 1:1 binding stoichiometry. From the titration data based on the 1:1 binding model, the association constant (K_a) for binding of **L7-Ni** and K^+ ions was calculated to be 6.6×10^5 M^{-1} using non-linear regression analysis by DynaFit (see Supporting Information).

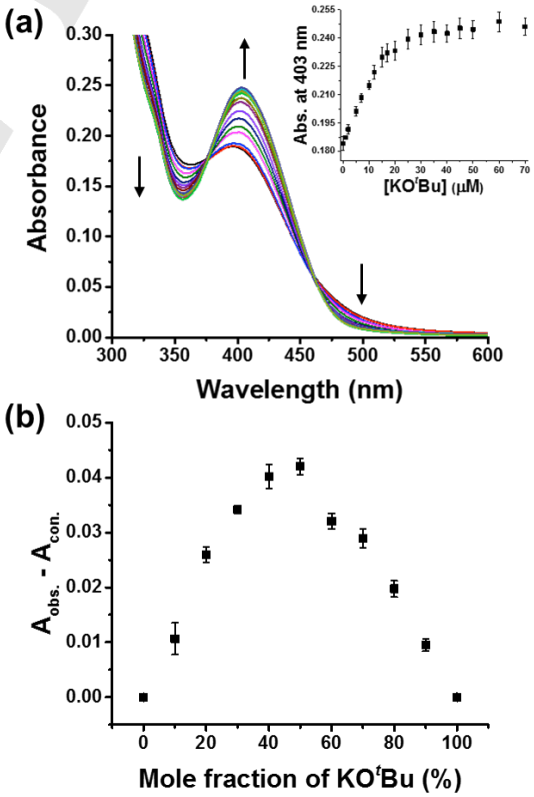


Figure 4. (a) UV-Vis spectra of L7-Ni (20 μM) in the presence of varying amounts of KO*t*-Bu (0 ~ 70 μM) in THF. Inset: Plot of absorbance at 403 nm *versus* concentration of KO*t*-Bu. (b) Job plot for binding mode between **L7-Ni** and K^+ ions in THF. A_{obs}: Absorbance of L7-Ni at 403 nm with varying amounts of KO*t*-Bu; [**L7-Ni**] + [KO*t*-Bu] = 40 μM, $A_{con.}$: Absorbance of **L7-Ni** (40 to 0 μM) at 403 nm without KO*t*-Bu.

In summary, we have developed cation-binding salen Ni catalysts for enantioselective alkynylation of trifluoromethyl ketones. The cation-binding Ni^{II}/K^{+} heterobimetallic catalyst plays a key role in promoting the alkynylation with substoichiometric base and open to air, resulting in high enantioselectivity (up to 97% ee) and yield (up to 99%). Additionally, we confirmed a 1:1 binding stoichiometry of the designed catalyst with K^{+} by UV-vis absorption spectroscopy. Further study of plausible mechanism and extension of reaction scope are ongoing.

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Keywords: Nickel • Bifunctional Catalysis • Alkynylation • Trifluoromethylketones

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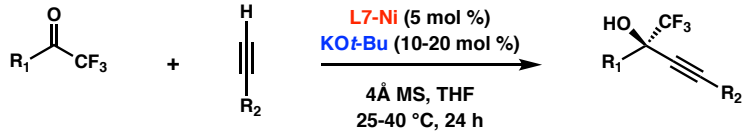
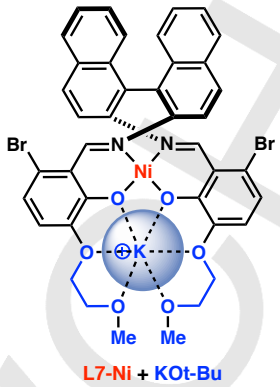
Ni-catalyzed Enantioselective Alkynylation via Bifunctional Catalysis:



R_1= aryl vinyl
R_2= aryl, cyclopropyl

up to 98% yield
and 97% ee
> 30 examples



Cation-binding salen nickel catalysts were developed for the enantioselective alkynylation of trifluoromethyl ketones in high yield (up to 99%) and high enantioselectivity (up to 97% ee). The reaction proceeds with substoichiometric quantities of base (10-20 mol% KO*t*-Bu) and open to air. UV-vis analysis revealed the pendant oligo-ether group of the catalyst strongly binds to the potassium cation (K^+) with 1:1 binding stoichiometry (K_a = 6.6×10^5 M^{-1}).

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