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Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2017 January 18.

Published in final edited form as:

Angew Chem Int Ed Engl. 2016 January 18; 55(3): 1070–1074. doi:10.1002/anie.201507494.

Nickel-Catalyzed Allylic Alkylation with Diarylmethane Pronucleophiles: Development and Mechanistic Insight

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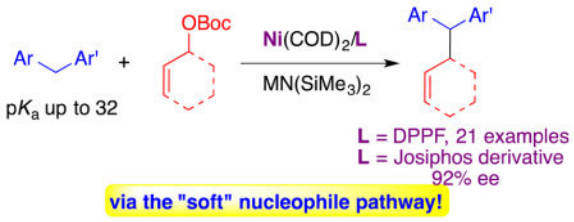
Abstract

Palladium-catalyzed allylic substitution reactions are among the most efficient methods to construct C–C bonds between sp^3-hybridized carbons. In contrast, much less work has been done with nickel catalysts. This may be due, in part, to the different mechanisms of allylic substitution reactions. Palladium catalysts generally undergo substitution via a “soft” nucleophile pathway, wherein the nucleophile attacks the allyl group externally. Nickel catalysts are usually paired with “hard” nucleophiles, which attack the metal before C–C bond-formation. Herein is introduced a rare nickel-based catalyst that promotes substitution with diarylmethane pronucleophiles via the “soft” nucleophile pathway. Preliminary studies on the asymmetric allylic alkylation are promising.

Graphical Abstract



Just a softy: Contrary to what would be predicted, organosodium nucleophiles derived from diarylmethane pronucleophiles are shown to behave as soft nucleophiles in Ni-catalyzed allylic substitution reactions. This general reaction (21 examples) is demonstrated to proceed by the double inversion pathway. A promising asymmetric version (92% ee) is demonstrated.

Keywords

Cross-Coupling; Asymmetric Catalysis

Metal-catalyzed allylic substitution reactions remain one of the most efficient approaches to construct C(sp^3)–C(sp^3) bonds. Among transition metal catalysts used in allylic

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substitutions, palladium has met with the greatest success. Many enantioselective palladium catalysts have been developed and elegantly applied to the synthesis of natural products.[1–6]

The mechanisms of allylic substitution reactions promoted by a variety of catalysts with different nucleophiles have been investigated.[1,2] From these studies, trends in reaction pathways have emerged and are now well accepted.[1] The reaction pathway has been found to depend on the nature of the nucleophile.[1] In general, anionic nucleophiles (Nu^-) are divided into two classes based on the pK_a of the pronucleophile, Nu–H: carbon nucleophiles derived from pronucleophiles with pK_a's < 25 are considered stabilized or "soft" nucleophiles while those from pronucleophiles with pK_a's > 25 are categorized as unstabilized or "hard" nucleophiles. The difference between these two classes is that soft nucleophiles attack the π-allyl moiety externally while hard nucleophiles bind directly to the metal center (*via* transmetallation) before C–C bond-formation with the allyl group (Scheme 1). Importantly, it has proven easier to control enantioselectivity with soft nucleophiles in Pd catalyzed asymmetric allylic alkylations (AAA) than with hard nucleophiles.[1,3,7–10] Thus, expanding the scope of soft nucleophiles in Pd-catalyzed AAA has attracted attention.[11–14]

In contrast to Pd-catalyzed allylic substitutions, which have been extensively used with soft nucleophiles, Ni catalysts have generally been paired with hard nucleophiles, such as Grignard reagents and other main group organometallics.[6,15–29] An advantage of nickel catalysts over palladium is their lower cost.

Early examples of nickel catalyzed allylic substitution reactions include Hiyama and coworkers use of (*S,S*)-chiraphos (Scheme 2A).[15] In a clever application of achiral ligands to optimize enantioselectivity,[30] Hoveyda and coworkers used the [(*S,S*)-chiraphos]Ni catalyst in the presence of PR_3 and Grignard reagents to develop a synthesis of enol ethers and ketones with high ee (Scheme 2B).[16] Consiglio and coworkers determined that EtMgBr attacked the nickel center (transmetallation) first followed by reductive elimination to form the product.[6,19] They found the excellent enantioselectivity with EtMgBr, but MeMgBr and (*n*-Pr)MgBr exhibited significantly lower enantioselectivities (Scheme 2C).[18] Unlike hard nucleophiles, soft nucleophiles in Ni-catalyzed AAA exhibit poor enantioselection (Scheme 2D). [31]

Our interest in the Tsuji-Trost reaction has been to expand the scope of soft nucleophiles. We recently demonstrated that diarylmethane pronucleophiles behave as soft nucleophiles in Pd-catalyzed allylic substitutions under basic conditions, raising the pK_a limit of soft nucleophiles from 25 to at least 32.[13] In the current study, we asked 1) if diarylmethane pronucleophiles were suitable substrates for Ni catalyzed allylic substitutions, 2) if they would react via the hard or soft nucleophile pathway, and 3) if highly enantioselective versions would be possible. Herein, we communicate that these basic nucleophiles react via the *soft nucleophile pathway* and disclose a promising preliminary Ni catalyzed AAA.

We initiated our study of the Ni-catalyzed allylic substitution by examining 24 of the most common mono and bidentate phosphine ligands with $Ni(COD)_2$, $KN(SiMe_3)_2$ and allylOBoc (see Supporting Information for details). DPPF was the most promising ligand [72% ^{1}H NMR assay yield (AY), Table 1, entry 1], outperforming van Leeuwen's Xantphos,

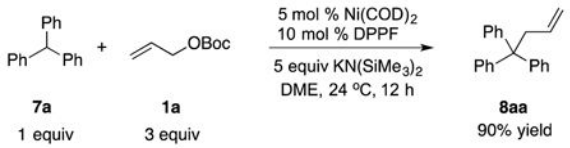
which was the ligand of choice in our Pd-catalyzed version of this reaction.[13,14] We then examined the nickel to ligand ratio, however, attempts to reduce the ligand loading led to lower yields (entries 2 and 3). DME proved to be a better solvent than THF, CPME (cyclopentyl methyl ether), dioxane and 2-MeTHF (entry 1 vs. 4–7). Nickel sources $NiCl_2$ and $NiBr_2$ resulted in decreased yields (entries 8 and 9 vs. 1). Finally, 88% isolated yield was obtained with 7.5 mol % Ni loading (entry 10).

With the optimized conditions in Table 1 (entry 10), we probed the scope of diphenylmethane derivatives (Table 2). The reaction with 4-fluoro diphenylmethane (**1b**) afforded the desired product **3ba** in 67% yield (entry 2). With 4-chloro and 4-bromo diphenylmethane $NaN(SiMe_3)_2$ proved to be a better base, providing products **3ca** and **3da** in 98% and 89% yield, respectively (entries 3–4). It is remarkable that generation of the Ni(π-allyl) is *faster* than the oxidative addition of C–Cl and C–Br bonds under our conditions. 4-Methyl diphenylmethane gave **3ea** in 61% yield (entry 5). Sterically hindered 2-methyl diphenylmethane reacted to provide **3fa** in 65% yield (entry 6). Fluorene derivatives are interesting components in material and photochemistry.[32] Due to the increased acidity of fluorene, 1.5 equiv LiO^{t}Bu could be used with 1.2 equiv of allylOBoc to provided **3ga** in 83% yield (entry 7). Unfortunately, due to the higher pK_a of 4-methoxy diphenylmethane, poor yields were obtained despite additional optimization.

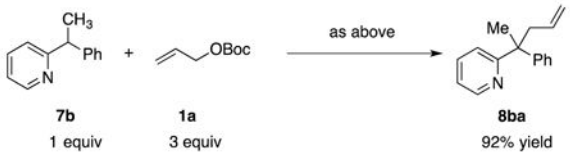
We next turned our attention to biologically relevant heterocyclic pronucleophiles (**4a–f**, Table 3). Pleasingly, a lower catalyst loading could be applied to these more acidic pronucleophiles. Pyridine containing diarylmethanes are useful in drug discovery.[33] 2-Benzylpyridine underwent coupling under the standard conditions to afford **5aa** in 91% yield (entry 1). Likewise, 3- and 4-benzylpyridine provided desired products **5ba** and **5ca** in 91% and 93% yield, respectively (entries 2 and 3). 3,3′-Dipyridylmethane was also a viable substrate, generating **5da** in 90% yield (entry 4). Thiophene containing products are important in agrochemicals and pharmaceuticals.[34] 2-Benzylthiophene rendered coupling product **5ea** in 82% yield (entry 5). Xanthene derivatives are building blocks for the synthesis of dyes.[32] Application of our standard reaction conditions to xanthene furnished **5fa** in 81% yield (entry 6).

Diallylation to construct quaternary carbon centers was achieved using excess allyl electrophile with 5 mol % Ni and 10 mol % DPPF (**4a–f**, Table 4). Presumably, the products could be cyclized using ring-closing metathesis.[35] 2-Benzyl, 3-benzyl, or 4-benzyl pyridine all gave good yields (75–84%, entries 1–3). 2-Benzylthiophene provided diallylation product **6da** in 83% yield under the standard reaction conditions. Fluorene and xanthene were also good substrates, leading to products in 89–90% yield (entries 5 and 6).

After exploring the diallylation, we wanted to determine if other tertiary C–H's could be allylated using our method. Thus, with triphenylmethane (**7a**), the allylated product **8aa** was isolated in 90% yield [Eq. (1)]. Similarly, 2-(1-phenylethyl)pyridine (**7b**) also underwent allylation to form **8ba** in 92% yield [Eq. (2)]. These initial results bode well for further development of Ni-catalyzed allylic substitutions.

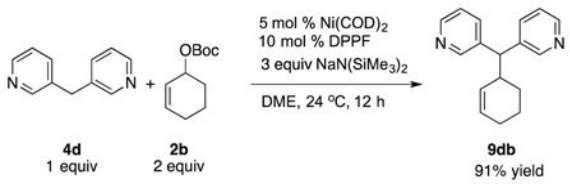


(1)



(2)

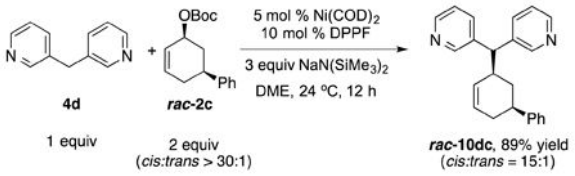
As outlined in the introduction, Ni-catalyzed allylic substitutions with hard nucleophiles, such as Grignard reagents, undergo reactions predominantly via transmetallation followed by reductive elimination (Scheme 1).[6,19] The nucleophiles employed in Tables 2–4 are organopotassium, -sodium, or -lithium derivatives, which would be predicted to undergo reaction via the hard nucleophile pathway. To probe this key step, we initially explored cyclic **2b** to determine if it was viable in nickel-catalyzed allylic substitution reactions. Thus, employing electrophile **2b** with $NaN(SiMe_3)_2$ afforded the substitution product **9db** in 91% yield [Eq. (3)].



(3)

To determine if the nucleophile derived from 3,3′-dipyridylmethane (**4d**) and $NaN(SiMe_3)_2$ behaves as a hard or soft nucleophile, we employed the stereoprobe ***rac*-2c** [Eq. (4)]. If the reaction proceeds with a single inversion, the *trans*-diastereomer will predominate, leading to the conclusion that reaction took place via the hard nucleophile pathway (Scheme 1). In contrast, formation of the *cis*-product would indicate a double inversion, where the nucleophile attacks the allyl moiety opposite the nickel (soft nucleophile pathway, Scheme 1). Conducting the allylic substitution under the standard conditions led to formation of the product **10dc** in 89% yield [Eq. (4)]. Analysis of the ^1H NMR coupling constants of the product[14] led to its assignment as the *cis*-diastereomer arising from a double inversion pathway. The stereochemistry of the product, therefore, indicates that the reaction proceeded by nucleophilic attack directly on the Ni(allyl) (soft nucleophile pathway). It is surprising

that this basic nucleophile behaves as a soft nucleophile with catalysts derived from either nickel or palladium.[13]



(4)

The AAA with diarylmethane pronucleophiles is challenging because selectivity is usually difficult to control with highly reactive nucleophiles. We therefore screened 178 enantioenriched mono and bidentate phosphine ligands with 3 equiv of base, 3,3′-dipyridylmethane and 2 equiv of cyclohexenyl-OBoc (**2b)** in the Ni-catalyzed AAA. We identified a Josiphos derivative (**L1**, Scheme 3) as the best hit with 75% assay yield and 70% ee. After optimization (see Supporting Information), we were able to obtain **9db** in 91% yield with 92% ee (Scheme 3A). Likewise, with the 7-membered ring ($n = 2$), we obtained the product 9dd in 85% yield with 92% ee. In order to determine if this catalyst/nucleophile combination also reacts via the soft nucleophile pathway, we performed the reaction with stereoprobe ***rac*-2c**. We observed predominately *cis* product, which indicates the nucleophile reacts by the soft nucleophile pathway (Scheme 3B).

In summary, we have developed the first Ni-catalyzed allylic alkylation with diarylmethane pronucleophiles. The protocol is robust with different nucleophiles including diphenylmethane derivatives and heteroaryl containing diarylmethanes. We have demonstrated that this method can be used to construct quaternary centers. In addition, the first Ni-catalyzed asymmetric allylic alkylation (AAA) of soft nucleophiles with high ee has been demonstrated. These results indicate that Ni-catalyzed asymmetric allylic alkylation (AAA) is not limited to hard nucleophiles and that this area warrants further investigation and development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (NIGMS 104349) and National Science Foundation (CHE-1464744) for financial support. H.J. thanks China Scholarship Council [201406350156] for financial support.

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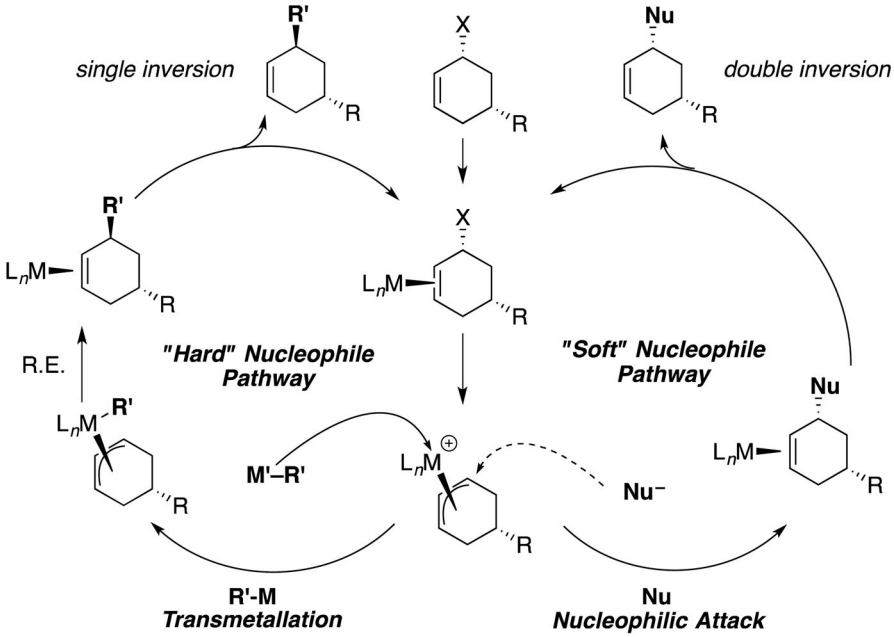
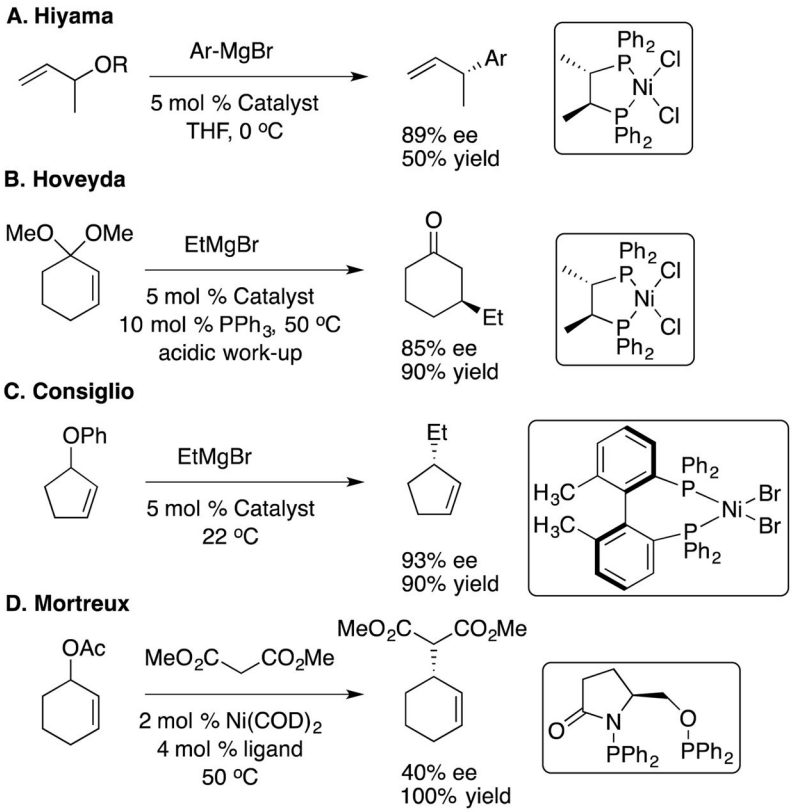
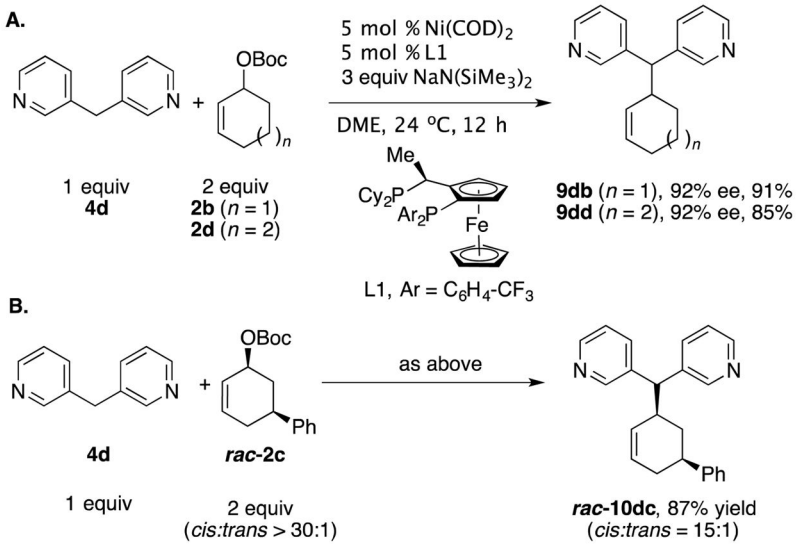


Scheme 1.
Mechanism of Transition Metal Catalyzed Allylic Substitution



Scheme 2.
Previous Ni-Catalyzed Asymmetric Allylic Alkylation Reactions.

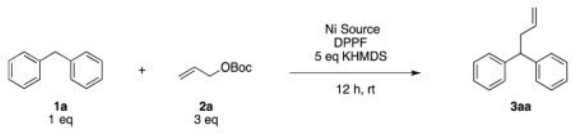


Scheme 3.

Asymmetric Allylic Alkylation and Mechanistic Study with **L1.**

Table 1

Optimization of Allylic Alkylation with Diphenylmethane **1a.**[a]



Entry	Ni Source	Ni/DPPF (mol %)	Solvent	Yield[b] (%)
1	$Ni(COD)_2$	5/10	DME	72
2	$Ni(COD)_2$	5/5	DME	39
3	$Ni(COD)_2$	5/7.5	DME	46
4	$Ni(COD)_2$	5/10	THF	46
5	$Ni(COD)_2$	5/10	CPME	<5
6	$Ni(COD)_2$	5/10	dioxane	<5
7	Ni(COD)2	5/10	2-Me-THF	52
8	$NiCl_2$	5/10	DME	35
9	$NiBr_2$	5/10	DME	51
10	$Ni(COD)_2$	7.5/15	DME	90 (88)[c]

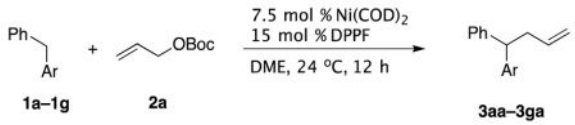
[a] Reactions conducted on a 0.1 mmol scale.

[b] Yields determined by ^1H NMR spectroscopy of the crude reaction mixtures.

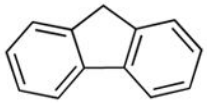
[c] Isolated yield after chromatographic purification.

Table 2

Scope of Diarylmethanes in Allylic Alkylation Reactions.[a]



1a–1g 2a 3aa–3ga

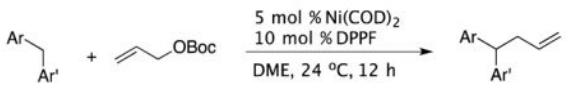
Entry	Ar	Base	Ratio (1:base:2a)	Product	Yield (%)
1	Ph	KHMDS	1:5:3	**3aa**	88
2	4-C_6H_4-F	KHMDS	1:4:3	**3ba**	67
3	4-C_6H_4-Cl	NaHMDS	1:5:3	**3ca**	98
4	4-C_6H_4-Br	NaHMDS	1:5:3	**3da**	89
5	4-C_6H_4-Me	KHMDS	1:5:3	**3ea**	61
6	2-C_6H_4-Me	KHMDS	1:5:3	**3fa**	65
7		LiO^{t}Bu	1:1.5:1.2	**3ga**	83

[a]Reactions conducted on a 0.1 mmol scale.

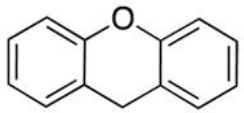
[b]Isolated yield after chromatographic purification.

Table 3

Scope of Heterocyclic Diarylmethanes in Allylic Alkylation Reactions.[a]



4a–f **2a** **5aa–5fa**

Entry	Ar	Ar′	Base	Ratio (4:base:2a)	Product	Yield (%)
1	2-Py	Ph	NaHMDS	1:2:1.2	**5aa**	91
2	3-Py	Ph	NaHMDS	1:3:1.2	**5ba**	91
3	4-Py	Ph	LiHMDS	1:2:1.2	**5ca**	93
4	3-Py	3-Py	LiHMDS	1:3:1.2	**5da**	90
5	2-thienyl	Ph	NaHMDS	1:2:1.2	**5ea**	82
6			LiHMDS	1:3:1.2	**5fa**	81

[a]Reactions conducted on a 0.1 mmol scale.

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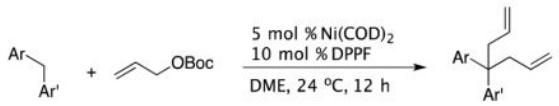
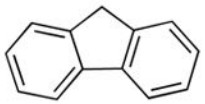
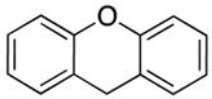
Table 4

Scope of Diallylation of Diarylmethanes



4a,b,c,e,f, 1g **2a** **6aa–6fa**

Entry	Ar	Ar′	Base	Ratio (4:base:2a)	Product	Yield (%)
1	2-Py	Ph	KHMDS	1:5:3	**6aa**	84
2	3-Py	Ph	KHMDS	1:5:3	**6ba**	78
3	4-Py	Ph	KHMDS	1:5:3	**6ca**	75
4	2-thienyl	Ph	KHMDS	1:5:3	**6da**	83
5			KO′Bu	1:5:3	**6ea**	90
6			NaHMDS	1:5:3	**6fa**	89

*[a]*Reactions conducted on a 0.1 mmol scale.

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