Asymmetric Catalysis

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

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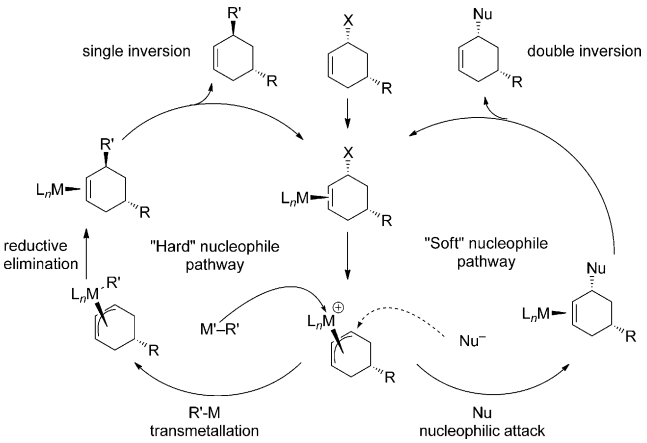
Abstract: *Palladium-catalyzed allylic substitution reactions are among the most efficient methods to construct C–C bonds between sp^3-hybridized carbon atoms. In contrast, much less work has been done with nickel catalysts, perhaps because of the different mechanisms of the allylic substitution reactions. Palladium catalysts generally undergo substitution by 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. Introduced herein is a rare nickel-based catalyst which promotes substitution with diarylmethane pronucleophiles by the soft-nucleophile pathway. Preliminary studies on the asymmetric allylic alkylation are promising.*

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 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 value of the pronucleophile (Nu–H): carbon nucleophiles derived from pronucleophiles with pK_a values less than 25 are considered stabilized or "soft" nucleophiles, while those from pronucleophiles with pK_a values greater than 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 (by transmetallation) before C–C bond formation with the allyl group (Scheme 1). Importantly, it has proven easier to control enantioselectivity with soft nucleophiles in palladium-catalyzed asymmetric allylic alkylations (AAAs) rather than with hard nucleophiles.[1,3,7–10] Thus expanding the scope of soft nucleophiles in palladium-catalyzed AAAs has attracted attention.[11–14] In contrast to palladium-catalyzed allylic substitutions, which have been extensively used with soft nucleophiles, nickel 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.



Scheme 1. Mechanism of transition metal catalyzed allylic substitution.

Early examples of nickel-catalyzed allylic substitution reactions include the work from Hiyama and co-workers who used (*S*,*S*)-chiraphos (Scheme 2a).[15] In a clever application of achiral ligands to optimize enantioselectivity,[30] Hoveyda and co-workers 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* values (Scheme 2b).[16] Consiglio and co-workers determined that EtMgBr attacked the nickel center (transmetallation) first with subsequent reductive elimination to form the product (Scheme 2c).[6,19] They found excellent enantioselectivity was obtained with EtMgBr, but MeMgBr and (*n*Pr)MgBr exhibited significantly lower enantioselectivities (Scheme 2c).[18] Unlike hard nucleophiles, soft nucleophiles in nickel-catalyzed AAAs generally exhibit poor enantioselection (Scheme 2d).[31]

Our interest in the Tsuji–Trost reaction has been to expand the scope with respect to soft nucleophiles. We recently demonstrated that diarylmethane pronucleophiles behave as soft nucleophiles in palladium-catalyzed allylic substitutions under basic conditions, thus 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 nickel-catalyzed allylic substitutions? 2) if they would react through the hard or soft-nucleophile

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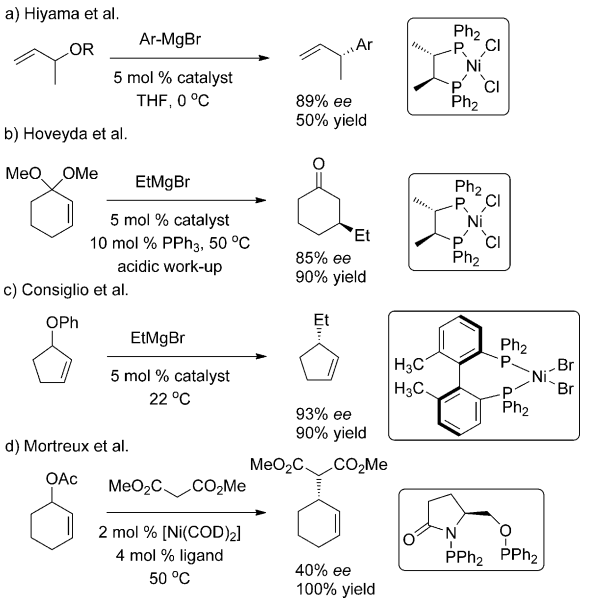
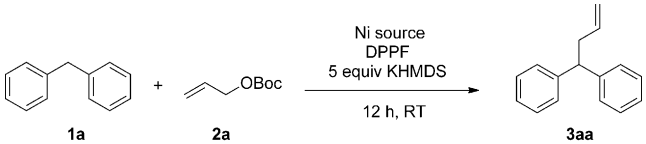


Scheme 2. Previous nickel-catalyzed asymmetric allylic alkylation reactions. COD = 1,5-cyclooctadiene, THF = tetrahydrofuran.

pathway? and 3) if highly enantioselective versions would be possible? Herein, we communicate that these basic nucleophiles react through the soft-nucleophile pathway and we disclose a promising preliminary nickel-catalyzed AAA.

We initiated our study of the nickel-catalyzed allylic substitution by examining 24 of the most common mono- and bidentate phosphine ligands with $[Ni(COD)_2]$, $KN(SiMe_3)_2$, and the Boc-protected allyl **2a** (see the Supporting Information for details). DPPF was the most promising ligand [72% ^{1}H NMR assay yield (AY); Table 1, entry 1], thus outperforming van Leeuwen's Xantphos, which was the ligand of

Table 1: Optimization of allylic alkylation with diphenylmethane (**1a**).[a]



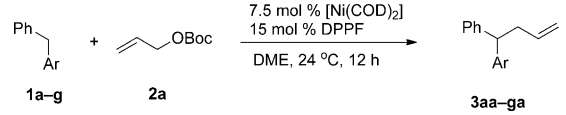
Entry	Ni Source	Ni/DPPF [mol %]	Solvent	Yield [%][b]
1	$[Ni(COD)_2]$	5:10	DME	72
2	$[Ni(COD)_2]$	5:5	DME	39
3	$[Ni(COD)_2]$	5:7.5	DME	46
4	$[Ni(COD)_2]$	5:10	THF	46
5	$[Ni(COD)_2]$	5:10	CPME	< 5
6	$[Ni(COD)_2]$	5:10	1,4-dioxane	< 5
7	$[Ni(COD)_2]$	5:10	2-Me-THF	52
8	$NiCl_2$	5:10	DME	35
9	$NiBr_2$	5:10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

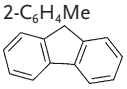
[a] Reactions conducted on a 0.1 mmol scale. [b] Yields determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] Yield of the product isolated after chromatographic purification. Boc = *tert*-butoxycarbonyl, DME = 1,2-dimethoxyethane, DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

choice in our palladium-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), 1,4-dioxane, and 2-MeTHF (entry 1 versus entries 4–7). Nickel sources such as $NiCl_2$ and $NiBr_2$ resulted in decreased yields (entries 8 and 9 versus entry 1). Finally, 88% yield of the isolated product was obtained with a 7.5 mol% nickel loading (entry 10).

With the optimized reaction conditions (Table 1, entry 10), we probed the scope with respect to the diphenylmethane derivatives **1** (Table 2). The reaction with 4-fluoro diphenylmethane (**1b**) afforded the desired product **3ba** in

Table 2: Scope with respect to the diarylmethanes in allylic alkylation reactions.[a]



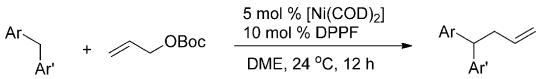
Entry	Ar	Base	**1**/base/**2a**	Product	Yield [%][b]
1	Ph	KHMDS	1:5:3	**3aa**	88
2	4-C_6H_4F	KHMDS	1:4:3	**3ba**	67
3	4-C_6H_4Cl	NaHMDS	1:5:3	**3ca**	98
4	4-C_6H_4Br	NaHMDS	1:5:3	**3da**	89
5	4-C_6H_4Me	KHMDS	1:5:3	**3ea**	61
6	2-C_6H_4Me	KHMDS	1:5:3	**3fa**	65
7		LiO*t*Bu	1:1.5:1.2	**3ga**	83

[a] Reactions conducted on a 0.1 mmol scale. [b] Yield of product isolated after chromatographic purification. HMDS = hexamethyldisilazide.

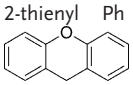
67% yield (entry 2). With 4-chloro- and 4-bromodiphenylmethane $NaN(SiMe_3)_2$ proved to be a better base, thus providing products **3ca** (98%) and **3da** (89%), respectively (entries 3 and 4). It is remarkable that generation of the Ni/π-allyl species is faster than the oxidative addition of C–Cl and C–Br bonds under our reaction 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 materials science and photochemistry.[32] Because of the increased acidity of fluorene, 1.5 equivalents of LiO*t*Bu could be used with 1.2 equivalents of **2a** to provide **3ga** in 83% yield (entry 7). Unfortunately, because of the higher pK_a value 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 reaction conditions to afford **5aa** in 91% yield (entry 1). Likewise, 3- and 4-benzylpyridine provided desired products **5ba** (91%) and **5ca** (93%), respectively (entries 2 and 3). 3,3′-Dipyridylmethane was

Table 3: Scope of heterocyclic diarylmethanes in allylic alkylation reactions.[a]



4a–f **2a** **5aa–fa**

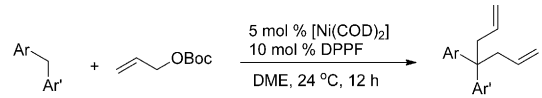
Entry	Ar	Ar′	Base	**4**/base/**2a**	Product	Yield [%][b]
1	2-Py	Ph	NaHMDS	1:2:1.2	**5aa**	91
2	3-Py	Ph	NaHMDS	1:3:1.2	**5ba**	91
3	4-Py	Ph	LiHMDS	1:2:1.2	**5ca**	93
4	3-Py	3-Py	LiHMDS	1:3:1.2	**5da**	90
5	2-thienyl	Ph	NaHMDS	1:2:1.2	**5ea**	82
6			LiHMDS	1:3:1.2	**5fa**	81

[a] Reactions conducted on a 0.1 mmol scale. [b] Yield of product isolated after chromatographic purification.

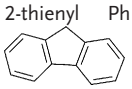
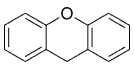
also a viable substrate, thus generating **5da** in 90% yield (entry 4). Thiophene-containing products are important in agrochemicals and pharmaceuticals.[34] 2-Benzylthiophene rendered the coupling product **5ea** in 82% yield (entry 5). Xanthene derivatives are building blocks for the synthesis of 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 an excess amount of the allyl electrophile with 5 mol % nickel and 10 mol % DPPF (**4a–c**, **4e**,**f**, and **1g**; Table 4). Presumably, the products could be cyclized using ring-closing metathesis.[35] 2-Benzyl, 3-benzyl, and 4-benzyl

Table 4: Scope of diallylation of diarylmethanes.



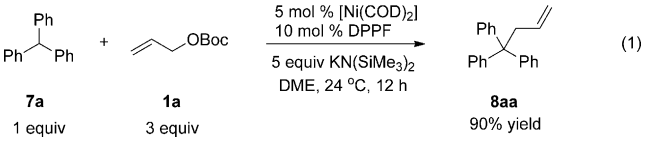
4a,b,c,e,f, 1g **2a** **6aa–fa**

Entry	Ar	Ar′	Base	**4**/base/**2a**	Product	Yield [%][b]
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*t*Bu	1:5:3	**6ea**	90
6			NaHMDS	1:5:3	**6fa**	89

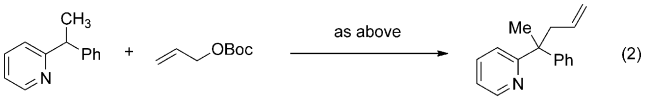
[a] Reactions conducted on a 0.1 mmol scale. [b] Yield of product isolated after chromatographic purification.

pyridine all gave good yields (75–84%, entries 1–3). 2-Benzylthiophene provided the diallylation product **6da** in 83% yield under the standard reaction conditions. Fluorene and xanthene were also good substrates, thus leading to products in 89–90% yield (entries 5 and 6).

After exploring the diallylation, we wanted to determine if other tertiary C–H moieties 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 nickel-catalyzed allylic substitutions.

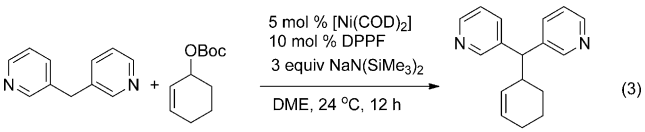


7a 1 equiv **1a** 3 equiv **8aa** 90% yield (1)



7b 1 equiv **1a** 3 equiv **8ba** 92% yield (2)

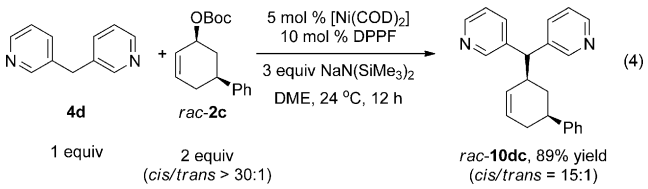
As outlined in the introduction, nickel-catalyzed allylic substitutions with hard nucleophiles, such as Grignard reagents, undergo reactions predominantly by transmetallation and subsequent reductive elimination (Scheme 1).[6,19] The nucleophiles employed in Tables 2–4 are organopotassium, organosodium, and organolithium derivatives, which would be predicted to undergo reaction through 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. By employing the electrophile **2b** with $NaN(SiMe_3)_2$ the substitution product **9db** was afforded in 91% yield [Eq. (3)].



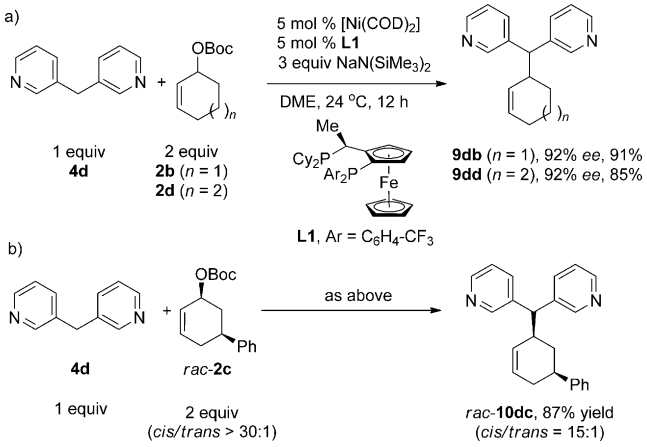
4d 1 equiv **2b** 2 equiv **9db** 91% yield (3)

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, thus leading to the conclusion that reaction took place through 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 reaction conditions led to formation of the product **10dc** in 89% yield [Eq. (4)]. Analysis of the ^{1}H NMR coupling constants of the product[14] led to its assignment as the *cis* diastereomer, thus 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 species (soft-nucleophile pathway). It is surprising that this basic nucleo-

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



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 equivalents of base, 3,3′-dipyridylmethane, and 2 equivalents of **2b** in the nickel-catalyzed AAA. We identified a Josiphos derivative (**L1**; Scheme 3) as the best



Scheme 3. Asymmetric allylic alkylation and mechanistic study with **L1**.

hit with 75 % assay yield and 70 % *ee*. After optimization (see the Supporting Information), we were able to obtain **9db** in 91 % yield with 92 % *ee* (Scheme 3a). Likewise, with the seven-membered ring ($n = 2$), we obtained the product **9dd** in 85 % yield with 92 % *ee*. To determine if this catalyst/nucleophile combination also reacts through the soft nucleophile pathway, we performed the reaction with the stereoprobe *rac*-**2c**. We observed predominately the *cis* product, which indicates the nucleophile reacts by the soft-nucleophile pathway (Scheme 3b).

In summary, we have developed the first nickel-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 nickel-catalyzed asymmetric allylic alkylation (AAA) of soft nucleophiles with high *ee* values has been demonstrated. These results indicate that nickel-catalyzed asymmetric allylic alkylation (AAA) is not limited to hard nucleophiles and that this area warrants further investigation and development.

Acknowledgments

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Keywords: allylic compounds · asymmetric catalysis · cross-coupling · nickel · synthetic methods

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