Synthetic Methods

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Asymmetric Cross-Coupling of Aryl Triflates to the Benzylic Position of Benzylamines**

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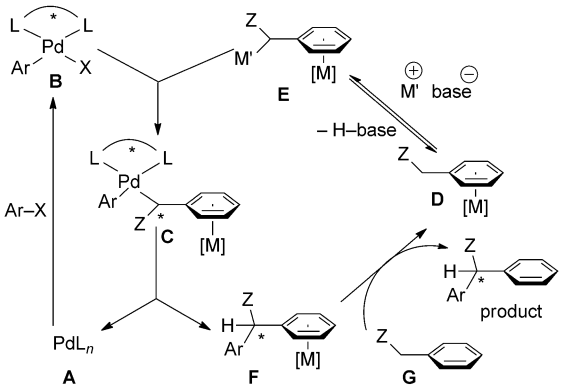
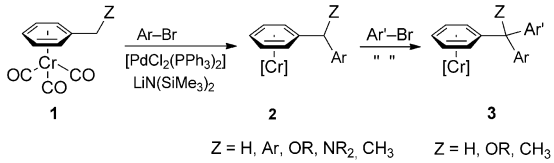
The development of new transition-metal-catalyzed cross-coupling methods has been a focus of intense research.[1] More recently, direct arylations are emerging as a more efficient method to C–C bond formations.[2] Certain types of C–H bonds, however, have proven difficult to arylate, and represent a particular challenge for asymmetric processes. We envisioned a novel and potentially very powerful dual catalyst cycle for the enantioselective functionalization of very weakly acidic benzylic C–H groups (Scheme 1). The left-hand cycle involves the palladium-catalyzed cross-coupling through oxidative addition to Pd^0, transmetallation with M′ of the organometallic intermediate **E** to generate **C** and reductive elimination to close the cycle. The right-hand cycle is initiated with reversible deprotonation of the activated benzylic CH groups of the η^6-arene complex to generate **E**. Emerging from the palladium-catalyzed cycle, arene exchange between **F** and free arene **G** liberates the product and regenerates **D**. To simplify the extremely challenging development of such a dual catalyst system, we separated it into three phases. In the first, we focused solely on the palladium-catalyzed left-hand cycle by selecting an arene-activating moiety, $\{Cr(CO)_3\}$, which would not undergo arene exchange (i.e., **F** does not react with **G**). This enabled the initial proof-of-concept cross-coupling, which is summarized in Scheme 2.[3] In the current phase of this project, we introduce the palladium-catalyzed enantioselective version of the reaction in Scheme 2, a reaction which proceeds by an unusual dynamic kinetic resolution (DKR). Future work (Phase 3) will focus on closing the right-hand cycle.[4]



Scheme 1. Dual catalyst cycle for the asymmetric benzylic functionalization process.



Scheme 2. Tricarbonylchromium-assisted synthesis of achiral and racemic polyarylmethanes.

Development of an enantioselective version of the coupling reaction to afford compounds like **2** in Scheme 2 was perceived to be particularly challenging because of some unique features of our proposed catalytic cycle. First, the diarylmethane-based products in Scheme 2 are more acidic than the starting materials, and might be expected to lead to racemization of the enantioenriched products. Second, our proposed mechanism, described in more detail below (Scheme 3), involves achieving enantioselectivity through a novel DKR.[5] This mechanism requires that one of the reversibly formed lithiated planar-chiral Cr adducts, either **1**-Li or **1**-Li′, undergoes transmetallation with the enantioenriched palladium catalyst much faster than the other. Together, these characteristics require identification of a chiral ligand/metal complex which is exquisitely tuned to promote the chemistry under mild reaction conditions.

Mechanistically, initial deprotonation of [(η^6-benzylamine)$Cr(CO)_3$] by $LiN(SiMe_3)_2$ was anticipated to be rapid based on the chemistry in Scheme 2.[3a] Because of the ability of $\{Cr(CO)_3\}$ to delocalize negative charge,[6] the lithiated intermediates **1**-Li and **1**-Li′ (Scheme 3) were expected to be planar chiral and configurationally stable owing to the partial double bond character between the *ipso* and benzylic carbon atoms.[7] We hypothesized that rapid and reversible deproto-

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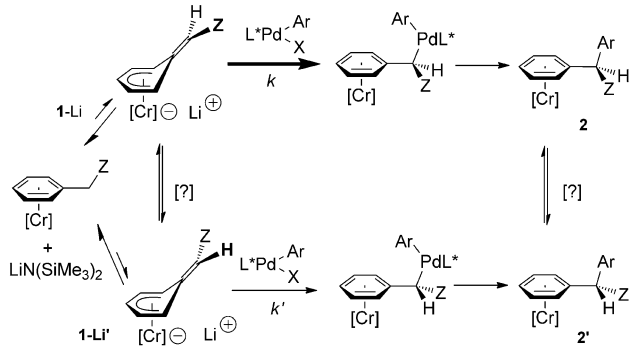
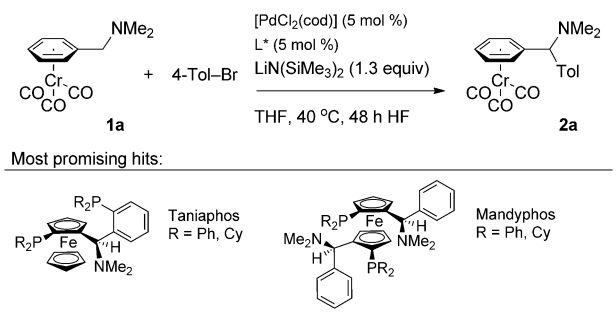


Scheme 3. Proposed asymmetric arylation of tricarbonylchromium-stabilized benzyllithiums showing the reversible deprotonation and interconversion of lithiated enantiomers, enantiodetermining transmetallation to palladium, and reductive elimination to form **2**.

nation of **1** by $LiN(SiMe_3)_2$ would provide a necessary pathway to equilibrate the enantiomers **1**-Li and **1**-Li′. In this proposed scenario, the enantiodetermining step would then be transmetallation of the enantiomers **1**-Li and **1**-Li′ with the enantioenriched Pd^{II} center. Given the high nucleophilicity of these organolithiums,[8] transmetallation is expected to be irreversible. At the same time, we were concerned that the high reactivity of **1**-Li and **1**-Li′ would render selective transmetallation of **1**-Li over **1**-Li′ difficult.

Considering the significant demands on the catalyst in this unusual DKR, it is quite likely that the number of promising, highly enantioselective ligands will be very small. Hedging our bets, we first examined the privileged bis(phosphine) 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap). Under the successful reaction conditions presented in Scheme 2, very low conversion and enantioselectivity were observed. Thus, our strategy for ligand discovery relied on low-barrier high-throughput experimentation (HTE), in which a large library of enantioenriched ligands could be screened at once on the microscale.[9]

The asymmetric coupling of the *N*,*N*′-dimethylbenzyl amine complex $[(\eta^6\text{-}Me_2NCH_2Ph)Cr(CO)_3]$ **1a**[10] with 4-bromotoluene using $LiN(SiMe_3)_2$ was examined in an HTE screen with a large collection (>190, see the Supporting Information for a complete list) of enantioenriched mono- and bidentate phosphine ligands (Scheme 4). Reactions were run in parallel in 250 μL HPLC vials on a 2 μmol scale (0.5 mg substrate). Although several ligands showed high conversion to product **2a** (by HPLC), only certain ferrocenyl phosphine ligands in the Taniaphos and Mandyphos family exhibited high *ee* values (≥80%). The Cy-Mandyphos-based (Cy = cyclohexyl) palladium catalyst exhibited the highest enantioselectivity, although conversion was low relative to Taniaphos. Interestingly, these selective catalysts are phosphine ligands which contain a tertiary amine. We hypothesize that the amino group is important in coordinating to planar-chiral **1**-Li or **1**-Li′ during the transmetallation step (Scheme 3). A similar hypothesis was made by Kumada and co-workers in the asymmetric cross-coupling of *s*BuMgBr with aryl bromides, although the reactions are quite different.[11]



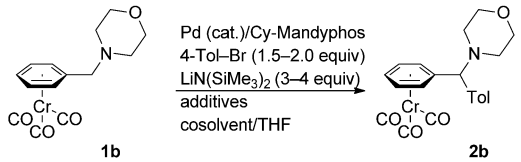
Scheme 4. Initial screen of chiral ligands for the asymmetric cross-coupling of **1a** with 4-bromotoluene to yield **2a**. cod = cyclo-1,5-octadiene, THF = tetrahydrofuran.

Unfortunately, attempts to increase conversion while maintaining high enantioselectivity proved difficult. Conducting the reaction at higher concentrations or with additional equivalents of base accelerated product decomposition. Lowering the temperature to increase enantioselectivity resulted in very low conversions. Furthermore, the product *ee* value eroded as the reaction progressed. To explore the possibility of product racemization, the benzylmorpholino complex **2b** was recrystallized to 94% *ee*. It was then heated at 40 °C with 4 equivalents of $LiN(SiMe_3)_2$ for 16 hours and quenched with D_2O. No detectable deuterium incorporation (^1H NMR) and negligible erosion of the *ee* value (<1%) were observed. Substrate **1b** was then used for further investigation.

We next examined the effects of solvent composition and additives. Use of toluene as a cosolvent (40%) led to an increase in enantioselectivity (up to 81% *ee*) and reduced product decomposition, although yields of the isolated product remained below 50%.

Amines and LiX salts are known to influence aggregation and reactivity of organolithium species,[12] and were examined next (Table 1, entries 3–8). Additionally, we hypothesized that amines could potentially influence the transmetallation

Table 1: Initial optimization of conditions in the asymmetric coupling reaction of **1b** with 4-bromotoluene.



	Additives (equiv)	Cosolvent (%)[a]	*T* [°C]	*t* [h]	Conv. [%][b]	*ee* [%]
1	–	–	50	9	95	55
2	–	tol (40)	40	9	62	81
3	iPr_2NEt (2)	tol (40)	40	9	56	82
4	TEEDA (2)	tol (40)	18	12	58	75
5	TMEDA (2)	tol (40)	18	40	41	91
6	TMEDA (1)	tol (40)	18	40	38	86
7	PMDTA (1)	tol (40)	18	48	60	77
8	PMDTA (2)	tol (40)	18	42	35[c]	90

[a] Reactions were run at 0.08–0.1 M [**1b**]. [b] The conversion was determined by SFC. [c] Yield of isolated product. TEEDA = *N*,*N*,*N*′,*N*′-tetraethylethylenediamine

and, therefore, enantioselectivity, by binding to organolithium intermediates. Indeed, polydentate tertiary amines accelerated the coupling, thus allowing reactions to proceed at 18 °C (entries 4–8). Furthermore, 2 equivalents of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) led to an increase in enantioselectivities up to 91 % (entries 5 and 8). Lithium chloride, bromide, and iodide additives[13] had a detrimental effect on enantioselectivity, presumably impacting the transmetallation (see the Supporting Information for details). Thus, generation of a LiBr by-product during the reaction with aryl bromides may be responsible for the erosion of the *ee* value with increasing conversion as outlined earlier for reactions using **1a** in the absence of TMEDA or PMDTA. We have previously demonstrated that the negative impacts of LiCl on enantioselective reactions can be counteracted by sequestering the salt with polydentate amines.[14]

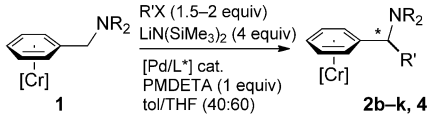
To circumvent the detrimental effects of LiBr altogether, other ArX derivatives were examined (Table 2, entries 1–3). 4-Tolyl triflate resulted in much faster and cleaner formation

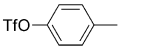
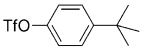
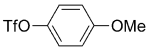
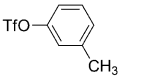
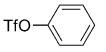
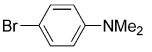
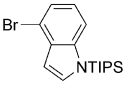
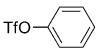
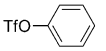
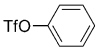
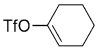
Table 2: Effect of electrophile leaving group in the asymmetric coupling reaction of 4-Tol-X with **1b** to yield **2b**.

	X	Additives (equiv)[a]	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%]
1	Cl	TMEDA (2)	35	24	–	–
2	OTs	PMDTA (1)	50	24	–	–
3	OTf	PMDTA (2)	18	7	80	81
4	OTf	PMDTA (1)	18	12	80	87
5	OTf	PMDTA (1)	5–10	48	73	89
6	OTf	–	18	12	18[c]	79
7[d]	OTf	–	18	12	23[c]	63
8	OTf	PMDTA (1), PhCl (2%)	18	8	76	92

[a] Unless otherwise stated, reactions were run at 0.08–0.1 M. [**1b**] in 40:60 toluene/THF as the solvent. [b] Yields of isolated products unless otherwise specified. [c] The conversion was determined by SFC. [d] Reaction in THF without toluene. Tf = trifluoromethanesulfonyl.

Table 3: Scope of the cross-coupling of tertiary benzylamine and R′X using optimized reaction conditions.[a]



	NR_2	R′X	Product	*T* [°C][b]	*t* [h]	Yield [%][c]	*ee* [%]
1			**2b**	RT	8	76	92
2[c]			**2c**	0→RT	24	74	90
3[c]			**2d**	0→RT	18	72	87
4[c]			**2e**	0→RT	20	72	90
5			**2f**	0→RT	16	80	89
6[d]			**2g**	RT	60	59	84
7[d]			**2h**	RT	48	36	62
8			**2i**	0→RT	24	66	87
9[d]			**2j**	8–10	60	72	85
10			**2k**	0→RT	24	69	88
11			**4**	0→RT	18	80	53

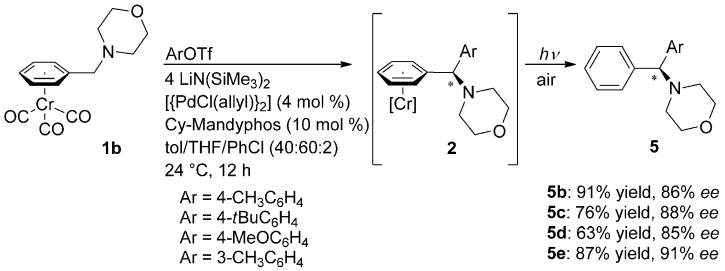
[a] Reaction conditions: **1** (1 equiv; 0.08–0.1 M [**1b**]), $LiN(SiMe_3)_2$ (4 equiv), R′X (1.5–2 equiv), [{PdCl(allyl)}$_2$] (2–2.5 mol%), Cy-Mandyphos (12 mol%), tol/THF (40:60), PhCl (2 vol%), PMDTA (1 equiv). [b] RT is typically 18–19 °C. [c] Reported yields and *ee* values are the average for two runs. [d] For reactions using ArBr or benzyl piperidine, PhCl was not used. TIPS = triisopropylsilyl.

of the product with only a slightly lower *ee* value at room temperature (entry 3). By decreasing the amount of PMDTA (entries 4–7) and employing 2 % chlorobenzene as a solvent additive, an increase in the product *ee* value was observed: up to 92 % with a much-improved yield (76 %; entry 8). Note that chlorobenzene is unreactive under these reaction conditions, and its role in the reaction is currently under investigation.

Using the reaction conditions as given for entry 8 in Table 2, the scope of the asymmetric coupling reaction was next examined. Electron-rich aryl triflates were good substrates (Table 3, entries 1–6). Unfortunately, electron-poor substrates were less compatible with these reaction conditions. For example, 3-$CF_3C_6H_4$OTf triflate formed benzyne under the basic reactions conditions (see the Supporting Information) and 3-pyridyl triflate gave no product. Aryl triflates with *ortho*-methyl or *ortho*-methoxy substituents exhibited less than 5 % conversion. In contrast, the *ee* value was relatively insensitive to the nature of amine substitution. Reactions using piperazino, piperidino, and *N*,*N*-dimethylamino derivatives (entries 8–10) behaved similarly to the morpholino substrate (entry 5). Cyclohexenyl triflate (entry 11) exhibited good reactivity but moderate enantioselectivity (53 %). Given that transmetallation to [L*PdR(OTf)] is enantiodetermining, it is not surprising that changing from R = Ph to R = cyclohexenyl has a significant impact on the product *ee* value.

Enantioenriched chromium-coordinated diarylmethylamines did not suffer a significant decrease in *ee* value upon demetallation. A solution of the purified complex may be exposed to sunlight and air and then filtered to obtain diarylmethylamine product. Alternatively, the concentrated crude arylation reaction mixture can be directly decomplexed and then purified by chromatography. The crude reaction mixtures for **2b–e** furnished the chromium-free diarylmethylamines **5b–e** in 63–91 % yields upon isolation with 85–91 % *ee* (Scheme 5).

The absolute configuration of **2b** using the (+)-enantiomer of Cy-Mandyphos was obtained by single-crystal X-ray diffraction and found to be *R* (see the Supporting Information).[15]



Scheme 5. One-pot arylation/decomplexation allows access to enantioenriched diarylmethylamines.

In summary, a novel dynamic kinetic resolution involving palladium-catalyzed cross-coupling of aryl triflates with [(η^6-benzylamine)$Cr(CO)_3$] has been presented. Diastereoselective transmetallation of one enantiomer of a rapidly equilibrating planar-chiral secondary benzyllithium species is likely the enantioselectivity-determining step in this process.

It is noteworthy that enantioenriched diarylmethylamines are core structures present in several current pharmaceuticals[16] and our approach to them represents a novel disconnection. Although this chemistry does not yet constitute a practical synthesis of these valuable compounds, this strategy and the conceptual understanding gained herein is critically important for future development of the dual catalyst enantioselective functionalization of weakly acidic C–H bonds.

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[15] CCDC 869404 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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