Communication

Asymmetric Synthesis of QUINAP via Dynamic Kinetic Resolution

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Asymmetric Synthesis of QUINAP via Dynamic Kinetic Resolution

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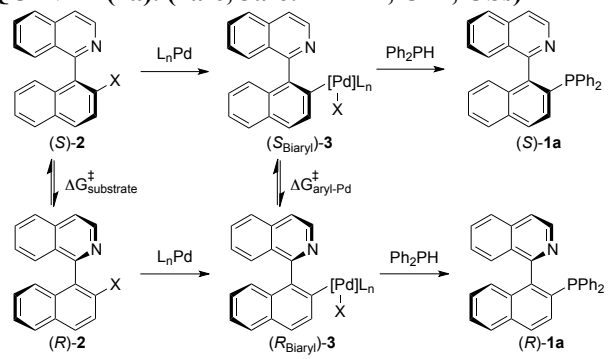
Supporting Information Placeholder

ABSTRACT: A palladium-catalyzed, atroposelective C–P coupling process has been developed for the asymmetric synthesis of QUINAP and its derivatives in high enantiomeric excess. Bromide, triflate (OTf) and 4-methanesulfonylbenzenesulfonate (OSs) precursors were studied, leading in the case of the triflate to a novel dynamic kinetic resolution involving isomerization of an arylpalladium intermediate. The operationally simple methods described in this communication afford these important ligands in good to high yields and selectivity using low catalyst loading (≤3 mol% Pd).

QUINAP (**1a**)[1] is one of the most useful chiral *P*,*N*-ligands in asymmetric catalysis and has found applications in several enantioselective reactions.[2] However, after many years since its discovery, synthetic methods for securing QUINAP in high enantiomeric excess still involve costly resolving agents[1a,b] or extended synthetic procedures.[3,4] We were interested in developing concise enantioselective methods that would provide QUINAP in optically pure form and be amenable to the synthesis of derivatives so as to support further advances in the field of *P*,*N*-ligand mediated catalysis.

Our strategy for the enantioselective synthesis of QUINAP (**1a**) involved investigation of atroposelective reactions of the known bromide[3] and triflate[1a] precursors (**2a** and **2b**) with diphenylphosphine in the presence of commercially available chiral bis(phosphine) ligands and a suitable palladium precursor (Scheme 1).[5,6] We hypothesized that in the case where neither the substrate (**2**) nor the intermediate (**3**) were subject to isomerization under the reaction conditions, and one of the two atropisomers of **2** reacted faster than the other, a kinetic resolution[7] pathway would be feasible for the synthesis of QUINAP. Moreover, the recovered enriched precursor **2** could be used for further manipulations. Alternatively, if the substrate (**2**) could undergo racemization under typical reaction conditions while one of the enantiomers selectively underwent phosphination, asymmetric synthesis of QUINAP would be achieved via dynamic kinetic resolution (DKR).[8] Finally, if the substrate racemization is too slow to achieve a standard DKR, isomerization of the arylpalladium intermediate (**3**) along the reaction pathway could prove to be a unique application of DKR in the asymmetric synthesis of QUINAP.

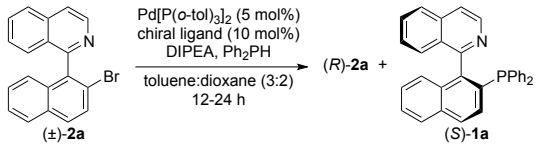
Scheme 1. Kinetic Resolution and DKR Syntheses of QUINAP (1a). (2a-c, 3a-c: X = Br, OTf, OSs)



Preliminary phosphination experiments involved the treatment of bromide **2a** with commercially available chiral bis(phosphine) ligands and Pd[P(*o*-tol)$_3$]$_2$. We were delighted to find that at 5 mol% Pd(0), 10 mol% ligand and 1.5 equivalents of diphenylphosphine, several ligands afforded high levels of enantioenrichment for both the recovered bromide **2a** as well as the product QUINAP (**1a**), suggesting high selectivity factors[9] for the desired reaction (Table 1). Early results indicated that bidentate ligands bearing dialkylphosphino groups were the best choices for this reaction and proceeded at 80–90 ºC (entries 4 and 8) while the less electron rich ligands having diarylphosphino groups were often weakly reactive and required higher temperature (entries 1–2). Moreover, at elevated temperatures, side reactions including hydrodebromination of **2a** led to lower yields and were therefore not further pursued.

Ligand (*S*,*S*)-**4** displayed unique reactivity for this reaction (Table 1, entry 4) and improved dramatically both in rate and selectivity upon the addition of tetra-*n*-butylammonium bisulfate.[11] Thus, under the optimized conditions (Table 2, entry 1),[12] a preparative gram-scale reaction of racemic bromide **2a** required only 0.5 mol% Pd(0) catalyst and afforded (*S*)-**1a** (95% ee) with recovered bromide (*R*)-**2a** (96% ee), both of which were easily recrystallized to >99.5% ee. A selectivity factor of 154 is consistent with these results.

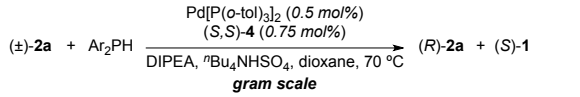
Table 1. Kinetic Resolution of Bromide 2a[a]



entry	temp. (°C)	chiral ligand[b]	% conv.[c]	(*R*)-**2a** ee[d,e]	(*S*)-**1a** ee[d,e]	*s*[f]
1	100	(*R*)-BINAP	55	54	10	1.8
2	100	(*R*)-DM-Segphos	100	--	4	--
3	100	(*R*,*R*)-^{i}Pr-BPE	60	96	46	9.6
4	80	(*S*,*S*)-Me-Ferrocelane [(*S*,*S*)-**4**]	47	>96	84	>44
5	90	(*S*,*S*)-Et-Ferrocelane	60	>96	54	>12
6	90	(*S*,*S*)-^{i}Pr-Ferrocelane	NR	ND	--	--
7	80	(*R*,S_{Fc})-Josiphos SL-J003-1 [(*R*,S_{Fc})-**5**]	77	72	12	2.3
8	90	(*S*,*S*)-Me-DuPhos [(*S*,*S*)-**6**][g]	43	88	90	55
9	90	(*S*,*S*)-Et-DuPhos [(*S*,*S*)-**7**]	53	54	66	8.3
10	100	(*S*,*S*)-^{i}Pr-DuPhos [(*S*,*S*)-**8**]	58	–80	–44	5.9
11	100	(*S*,*S*,*R*,*R*)-TangPhos	55	–78	–70	13.1
12	100	(*R*,*R*,*S*,*S*)-DuanPhos	50	–28	–76	9.6

[a]Reactions were performed with indicated amounts of Pd and ligand, 2.0 equiv. Ph_2PH, and 4.0 equiv. of DIPEA. [b]See reference 10. [c]Determined by UHPLC-MS analysis. [d]Determined by chiral SFC methods. [e]Negative ee values represent (*S*)-**2a** and (*R*)-**1a** predominating. [f]See reference 9. [g]10 mol% Pd and 20 mol% ligand was required. NR = no reaction. ND = not determined.

Table 2. Preparative Kinetic Resolution of 2a[a]



entry	Ar	% conv.[b] (time)	recovered **2a**[c]	product (**1**)[c]	*s*[d]
1	Ph	50 (20 h)	96% ee, 47% yield (99.7% ee, 44% yield)[e]	(*S*)-**1a** 95% ee (99.5% ee, 45% yield)[e]	154
2	*p*-tol	50 (14 h)	96% ee, 44% yield	(*S*)-**1b** 92% ee, 46% yield[f]	94
3	*p*-CF_3-C_6H_4	45 (26 h)	75% ee, 51% yield	(*S*)-**1c** 63% ee, 41% yield[f]	52
4	*o*-tol[g]	30 (48 h)	36% ee	(*S*)-**1d** 26% ee	16

[a]Reactions were performed with 1.0 equiv. ^{n}Bu$_4$NHSO$_4$, 1.5 equiv. Ar_2PH, and 4.0 equiv. of DIPEA. [b]Determined by UHPLC-MS analysis. [c]ee determined by chiral SFC methods. [d]See reference 9. [e]After recrystallization. [f]**1b-c** were found to be foams and could not be further enriched via recrystallization. [g]3.0 mol% Pd and 4.5 mol% (*S*,*S*)-**4** was used; **1d** and **2a** were inseparable by chromatography and crystallization methods.

We believe that this highly selective kinetic resolution operates by an atroposelective oxidative addition of the aryl bromide to the C_2-symmetric bis(phosphine)-Pd(0) complex.[13] In the case of (*S*,*S*)-**4**, the (*S*)-atropisomer of **2a** would be the preferred antipode to generate an arylpalladium bromide complex with minimal steric interactions between the aryl group and ligand as shown in Figure 1.

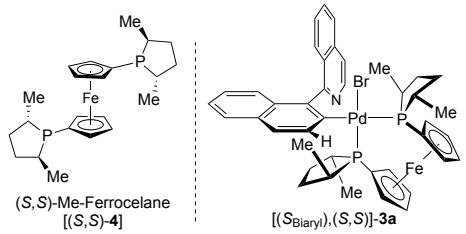
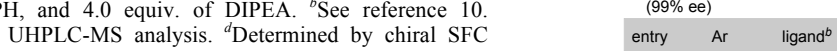


Figure 1. Proposed Intermediate 3a from Bromide (*S*)-2a and Pd Catalyst with (*S*,*S*)-4

Application of these conditions to the synthesis of QUINAP derivatives **1b-d** afforded less favorable outcomes (Table 2, entries 2–4). Although bis(*p*-tolyl)phosphine (entry 2) produced results similar to entry 1, bis(*p*-trifluoromethylphenyl)phosphine reacted with lower selectivity (entry 3). Additionally, neither of the two derivatives (**1b-c**) was found to be crystalline and hence could not be further enriched. Despite the higher catalyst loading required in the case of bis(*o*-tolyl)phosphine, the corresponding QUINAP derivative **1d** was obtained with poor selectivity (entry 4).

We therefore hoped that access to the derivatives **1b-d** in higher enantiomeric excess would be achievable by coupling to the optically pure bromide (*R*)-**2a** produced by the aforementioned kinetic resolution. In practice, we found that achiral or racemic ligands suffered low stereo-fidelity in the C–P coupling reaction with (*R*)-**2a** (Table 3, entries 1–2). Only (*R*,*R*)-**4** was effective in producing (*R*)-**1a** in 99% ee and also offered an improvement in the preparation of derivatives (*R*)-**1c** and (*R*)-**1d** (entries 3–5).

Table 3. C–P Coupling with Resolved (*R*)-2a[a]



entry	Ar	ligand[b]	time (h)	product (**1**)[c]
1	Ph	dcypf	20	(*R*)-**1a** 32% ee
2	Ph	*rac*-BINAP	20	(*R*)-**1a** 80% ee
3	Ph	(*R*,*R*)-**4**	20	(*R*)-**1a** 99% ee (98% yield)
4	*p*-CF_3-C_6H_4	(*R*,*R*)-**4**	48	(*R*)-**1c** 86% ee (98% yield)
5	*o*-tol[d]	(*R*,*R*)-**4**	72	(*R*)-**1d** 82% ee (85% yield)

[a]Reactions were performed under the conditions used in Table 2, entry 1. [b]See reference 10. [c]Determined by chiral SFC methods. [d]3.0 mol% Pd and 4.5 mol% (*R*,*R*)-**4** was used.

Encouraged by the efficiency of the kinetic resolution of **2a** at 70 °C terminating near 50% conversion, we were eager to investigate the possibility of developing a DKR by extending the reaction time and/or elevating the temperature. Upon measurement of racemization rates for the bromide **2a** and the product **1a**, it was apparent that the bromide **2a** required a higher temperature for racemization than the product QUINAP (**1a**) (Table 4, entries 1–2).[14] Further analysis of the racemization rates of sulfonate esters revealed that the 4-methanesulfonylbenzenesulfonate[15] derivative **2c** offered some opportunity for the DKR synthesis of **1a**.

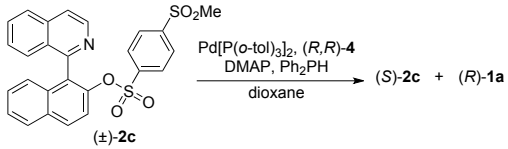
Table 4. Racemization Rates of 1a and 2a-c

entry	substrate	X	solvent (°C)	k_{epi} (s^{-1})	$t_{1/2}^{rac}$ (h)
1	**2a**	Br	mesitylene (150)	1.2 x 10^{-6}	78
2	**1a**	PPh_2	mesitylene (150)	1.8 x 10^{-4}	0.5
3	**1a**	PPh_2	toluene (90)	3.9 x 10^{-7}	246
4	**2b**	OTf	toluene (90)	1.6 x 10^{-6}	62
5	**2c**	OSs	toluene (90)	5.7 x 10^{-6}	17
6	**2b**	OTf	toluene (80)	5.2 x 10^{-7}	187
7	**2b**	OTf	dioxane (80)	4.2 x 10^{-6}	230

In contrast to the unreactivity of tosylate and mesylate derivatives in this reaction, we were pleased to find that sosylate **2c** reacted similarly to bromide **2a** in the standard kinetic resolution with (*R*,*R*)-**4** at 80 °C (Table 5, entry 1). However, securing a useful DKR with **2c** was found to be very difficult. Reaction of sosylate **2c** in dioxane at 90 °C required 4 days for complete consumption of the starting material. Upon isolation and purification, (*R*)-**1a** was obtained with only 43% yield and 56% ee (Table 5, entry 2). We observed that the extended reaction time at 90 °C led to nucleophilic deprotection of the sulfonate group of **2c**, resulting in lower yield.[16] The enantioselectivity of the C–P coupling suffered erosion and the product **1a** was subject to racemization at 90 ºC. Nevertheless, we hope that the as yet unreported reactivity of sosylate esters such as **2c** in palladium-catalyzed cross-coupling reactions might

assist other researchers in cases where a need for an alternative to the triflate ester arises.

Table 5. Kinetic Resolution and DKR with 2c.[a]

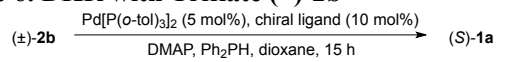


entry	temp. (°C)	Pd mol%	% conv.[b] (time)	recovered (*S*)-**2c**[c]	product (*R*)-**1a**[c]
1	80	2	55 (8 h)	96% ee (41% yield)	82% ee (39% yield)
2	90	8	95 (96 h)	ND	56% ee (43% yield)

[a]Reactions were performed with Pd to (*R*,*R*)-**4** ratio = 1:1.5, 1.5 equiv. of Ph_2PH and 4.0 equiv. of DMAP. [b]Determined by UHPLC-MS analysis. [c]ee determined by chiral SFC methods. ND = not determined.

Initial studies with the triflate **2b** using several commercially available ligands afforded poor to moderate enantioselectivities and conversions (Table 6). Once again, as seen for **2a**, electron-rich bidentate phosphine ligands, especially ferrocenyldialklphosphine ligands, showed remarkable reactivity for this reaction (entries 5–11). Ligand (*S*,*S*)-**4** proved to be a highly active catalyst for this substitution reaction, but afforded QUINAP (**1a**) with 0% ee (entry 5). Neither decreasing the temperature nor selection of bulkier variants of ligand (*S*,*S*)-**4** offered significant improvement (entry 6). Among the several Josiphos ligands that were tested, the enantiomeric excesses of the product **1a** were uniformly low (entries 7–9), except for SL-J003-1 [(*R*,S_{Fc})-**5**] which has both phosphines bearing cyclohexyl groups (entry 10). The C–P coupling reaction with (*R*,S_{Fc})-**5** proceeded with complete conversion affording (*S*)-**1a** in 60% ee. Interestingly, addition of tetra-*n*-butylammonium bromide (TBAB) to the reaction had the effect of reducing the selectivity to 8% ee (entry 11).

Table 6. DKR with Triflate (±)-2b[a]



entry	temp. (°C)	chiral ligand[b]	% conv.[c]	ee of **1a**[d,e]
1	70	(*S*,*S*)-Et-FerroTane	68	–4
2	90	(*S*,*S*,*R*,*R*)-TangPhos	75	58
3	80	(*R*,*R*,*S*,*S*)-DuanPhos	75	–4
4	80	(*S*,*S*)-Me-DuPhos [(*S*,*S*)-**6**]	NR	--
5	80	(*S*,*S*)-Me-Ferrocelane [(*S*,*S*)-**4**]	100	0
6	60	(*S*,*S*)-^{i}Pr-Ferrocelane	76	–30
7	80	(*R*,S_{Fc})-Josiphos SL-J001-1	100	24
8	80	(*R*,S_{Fc})-Josiphos SL-J004-1	100	14
9	80	(*R*,S_{Fc})-Josiphos SL-J009-1	100	8
10	80	(*R*,S_{Fc})-Josiphos SL-J003-1 [(*R*,S_{Fc})-**5**][f]	100	60
11	80	(*R*,S_{Fc})-Josiphos SL-J003-1 [(*R*,S_{Fc})-**5**][f,g]	100	8

[a]Reactions were performed with 1.5 equiv. of Ph_2PH, and 4.0 equiv. of DMAP. [b]See reference 10. [c]Determined by UHPLC-MS analysis. [d]Determined by chiral SFC methods. [e]Negative ee values represent (*R*)-**1a** predominating. [f]Reaction was complete within 1 hour. [g]The reaction was performed with 1 equiv. of ^{n}Bu_4NBr. NR = no reaction.

Given the slow racemization rate of **2b** at 80 °C in dioxane (Table 4, entry 7) and the fact that the reaction was complete in only 1 hour (Table 6, entry 10), we believe that the reaction conditions are mediating a rapid isomerization somewhere along the reaction course. In order to learn more about the nature of this remarkable, albeit modest, enantioselectivity, the reaction was conducted using Josiphos (*R*,S_{Fc})-**5** and the resolved triflate isomers (*S*)-**2b** and (*R*)-**2b** at 40 °C and 80 °C. Gratifyingly, these experiments verified the high stereofidelity of the matched reaction (Table 7, entries 1 and 3) and the stereo-correcting nature of the unmatched reactions without racemization of the starting material (entries 2 and 4). In contrast to the kinetic resolution of bromide **2a**, the comparable rates of the two isomers of triflate **2b** in Table 7 indicate a non-selective oxidative addition by the catalyst system with (*R*,S_{Fc})-**5**.

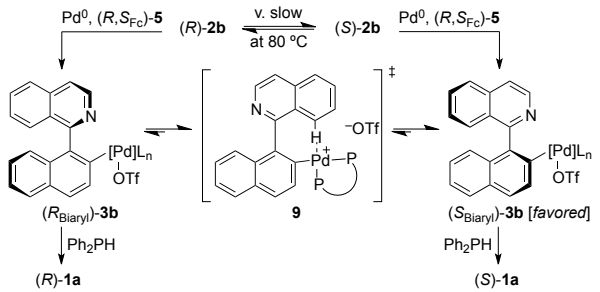
Table 7. C–P Coupling with Resolved Triflate 2b[a]

entry	substrate	temp. (°C)	% conv.[b] (time)	recovered substrate[c]	product **1a**[c]
1	(*S*)-**2b** 99% ee	40	71 (14 h)	(*S*)-**2b** 99% ee	(*S*)-**1a** 99% ee
2	(*R*)-**2b** 99% ee	40	67 (14 h)	(*R*)-**2b** 99% ee	(*R*)-**1a** 86% ee
3	(*S*)-**2b** 99% ee	80	82 (0.3 h)	(*S*)-**2b** 99% ee	(*S*)-**1a** 90% ee
4	(*R*)-**2b** 99% ee	80	60 (0.3 h)	(*R*)-**2b** 99% ee	(*R*)-**1a** 42% ee

[a]Reactions were carried out using 2.0 mol% Pd[(*o*-tol)$_3$P]$_2$, 3.0 mol% (*R*,S_{Fc})-**5**, 2.0 equiv. Ph_2PH and 4.0 equiv. of DMAP in dioxane. [b]Determined by UHPLC-MS analysis. [c]Determined by chiral SFC methods.

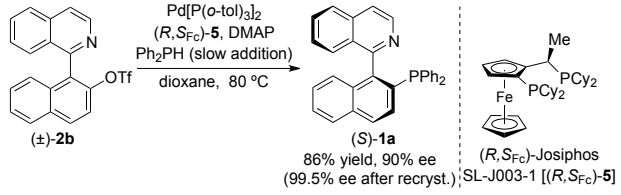
The rapid reaction rates observed with (*R*,S_{Fc})-**5** at 80 ºC requires that the lifetime of the arylpalladium triflate intermediate would necessarily be short. This indicates that a dramatically accelerated rate of isomerization (>4600-fold relative to racemization of **2b**) is operative during the lifetime of the arylpalladium intermediate. The labile nature of the triflate group in intermediate **3b** appears to facilitate the isomerization strongly favoring one diastereomeric structure (Scheme 2). Indeed, this ion-accelerated effect is supported by the fact that the observed enantiomeric excess of the product **1a** is lowered in the presence of added TBAB (Table 6, entry 11). In order to draw light to the possible origin of this favorable isomerization, we considered the recent work of Hartwig that demonstrated significant agostic interactions present in T-shaped arylpalladium(II) halide complexes using structures solved by X-ray diffraction.[17] In addition to noticing shorter M–H distances for the more electrophilic metal centers, Hartwig and coworkers postulated that the formally trivalent triflate complex could be depicted in a square planar geometry with an agostic M–H interaction occupying the otherwise vacant fourth coordination site.[18] It is likely that these effects are at play in our system also and can explain the favorable transition state for the isomerization of intermediate (R_{Biaryl})-**3b** where a stabilizing agostic interaction develops as the quinoline ring peri- hydrogen passes the cationic palladium atom in the chelated structure **9**. Our observations in this intriguing DKR presumably point to a kinetic manifestation of the agostic interactions of palladium intermediates.

Scheme 2. DKR via Isomerization of Arylpalladium Intermediate



Based on this mechanistic postulate, the overall effectiveness of the DKR was greatly improved by allowing more time for the isomerization of (R_{Biaryl})-**3b** to proceed before its subsequent reaction with diphenylphosphine. This was achieved by slow addition of diphenylphosphine over 4 hours to the reaction mixture containing triflate (±)-**2b**, 3.0 mol% Pd(0) and 4.5 mol% (R,S_{Fc})-**5** to obtain 86% yield of (S)-**1a** with 90% ee (Scheme 3).

Scheme 3. Optimized DKR of Triflate 2b



In conclusion, an atroposelective kinetic resolution and DKR strategy has been developed for the asymmetric synthesis of QUINAP (**1a**). Furthermore, the kinetic resolution pathway provides convenient access to enriched bromide **2a** and sosylate **2c** precursors. Our future endeavors in this area will investigate the structural nature of intermediates along the reaction course of the arylpalladium isomerization and explore the scope of atroposelective C–X coupling reactions for the synthesis of related *P*,*N*- and *N*,*N*-ligands.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Selectivity factor, s, was calculated from ee of **2a** and **1a** using the equation: $s = k_{fast}/k_{slow} = \ln[(1-c)(1-ee_{sm})]/\ln[(1-c)(1+ee_{sm})]$ where the value of c was taken as $c = ee_{sm}/(ee_{sm} + ee_{pdt})$. See reference 7(a).

(10) See SI for more information on ligands used in this study.

(11) Among the several $^nBu_4N^+$ salts that were surveyed as additives, bromide and bisulfate salts were found to be most effective.

(12) DIPEA, DMAP, and DABCO were superior bases than DBU, pyridine, 2,6-lutidine, *N*-methylmorpholine and Cs_2CO_3. **1a** itself was found to be a poor ligand for this reaction both in terms of rate and selectivity. $Pd[P(o\text{-}tol)_3]_2$ alone gave no background reaction.

(13) For examples of atroposelective oxidative addition, see: (a) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101; (b) Cho, Y.-H.; Kina, A.; Shimada, T.; Hayashi, T. *J. Org. Chem.* **2004**, *69*, 3811; (c) For atroposelective activation of C–H bonds, see: Kakiuchi, F.; Le Gendre, P.; Yamada, A.; Ohtaki, H.; Murai, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2647.

(14) See SI for a detailed study on racemization rates of **1a** and **2a-c**.

(15) We have assigned the name sosylate (abbreviated as –OSs) to denote the 4-methanesulfonylbenzenesulfonate group. To the best of our knowledge, this group has not previously been used in transition metal-catalyzed reactions. Sosylate **2c** was prepared using commercially available 4-methansulfonylbenzenesulfonyl chloride.

(16) The DKR reaction of **2c** at 90 ºC required rigorous exclusion of water. Replacing DMAP with less nucleophilic bases, like DIPEA, or the addition of 4Å MS offered no discernable improvement.

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