

Cross-Coupling

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Enantioconvergent Fukuyama Cross-Coupling of Racemic Benzylic Organozinc Reagents

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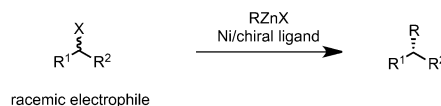
Abstract: The first enantioconvergent palladium-catalyzed Fukuyama cross-coupling of racemic benzylic organozinc reagents with thioesters has been developed. The reaction furnishes enantioenriched acyclic α -disubstituted ketone products in good yields and high enantioselectivities. A broad substrate scope is achieved under mild reaction conditions to prevent racemization of the potentially labile tertiary stereocenters.

Transition-metal-catalyzed cross-coupling reactions are among the most important methods for the preparation of complex organic molecules.^[1] Although the textbook reactions in this field deal with $C(sp^2)-C(sp^2)$ bond formation, the last five years have seen increased interest in the construction of bonds between sp^2 - and sp^3 -hybridized centers.^[2] In particular, the coupling of secondary alkyl fragments has been studied extensively because of the increased prevalence of such motifs in pharmacologically relevant molecules.^[3] For the cross-coupling of unsymmetrical secondary alkyl fragments, the possibility of achieving control of absolute stereochemistry would decisively increase synthetic utility and applicability. While Fu and co-workers have pioneered the stereoconvergent, asymmetric cross-coupling of secondary sp^3 -hybridized electrophiles (Scheme 1 a),^[4,5] considerably less work has been reported on the asymmetric coupling of secondary sp^3 -hybridized nucleophiles. Although Knochel and co-workers have reported several examples of diastereoconvergent cross-coupling of racemic nucleophiles (Scheme 1 b),^[6] the enantioconvergent cross-coupling of racemic organometallic reagents largely remains an unsolved problem in asymmetric synthesis.^[7] Up to now, only one nickel-catalyzed example of such a reaction is known.^[8]

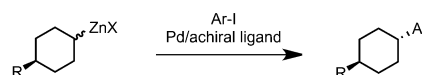
We hypothesized that rapid equilibration between the two enantiomers of a racemic secondary organometallic reagent^[9] could enable an appropriate chiral catalyst to react preferentially with one enantiomer by a dynamic kinetic resolution (DKR; Scheme 1 c).^[10,11]

The construction of enantioenriched acyclic α -disubstituted carbonyl compounds has been the subject of intense research. Currently, the vast majority of synthetic methods to prepare such compounds proceed via the intermediacy of

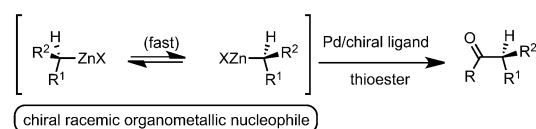
a) Nickel-catalyzed enantioconvergent cross-coupling of racemic electrophiles



b) Palladium-catalyzed diastereoconvergent cross-coupling



c) This work: palladium-catalyzed enantioconvergent cross-coupling of racemic nucleophiles



Scheme 1. Different strategies for diastereo- and enantioconvergent cross-coupling.

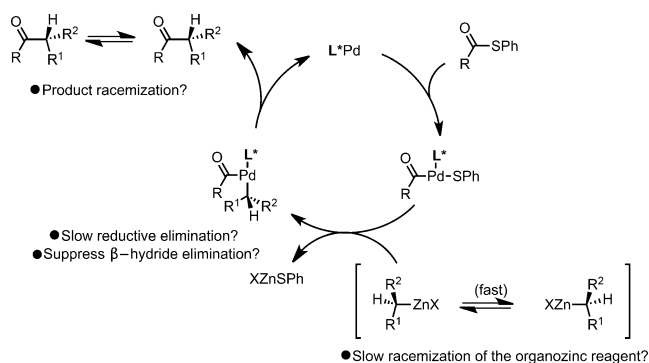
enolates or enolate equivalents.^[12] However, these strategies are not effective for the synthesis of enantioenriched α -disubstituted ketones because of the stringent requirement for site-selective enolization and the potential racemization of the newly formed stereogenic center under the reaction conditions. Transition-metal-catalyzed acyl cross-couplings can circumvent the difficulties described above, however, only one example of such a transformation has been described recently.^[13] Herein, we report a palladium-catalyzed cross-coupling of thioesters with racemic benzylic organozinc reagents as an approach for the construction of acyclic α -disubstituted ketones with high yields and enantioselectivities.

Scheme 2 depicts the associated challenges for the development of such a reaction. Our first concern was that the rate of racemization of the organozinc reagent should be fast enough to achieve an effective DKR. Studies have shown that under ambient conditions, chiral cyclic and acyclic organozinc halides appear to be configurationally stable,^[14] however, secondary benzylic organozinc halides have been found to racemize more rapidly.^[10,15] The second concern was the selection of an appropriate chiral ligand, which does not only select preferentially one of the two enantiomers of the organozinc reagent, but also enforces a fast reductive elimination (whilst suppressing deleterious β -hydride elimination) to prevent any racemization of the key alkylpalladium species.^[16]

We started our investigations with the cross-coupling of a simple thioester substrate, **1a**, with (1-phenylethyl)zinc

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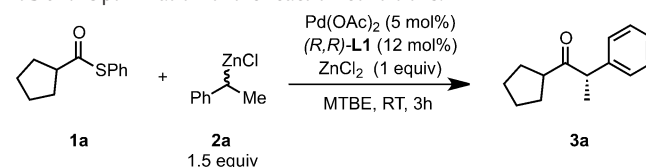
Scheme 2. Catalytic cycle and associated challenges in the enantioconvergent palladium-catalyzed Fukuyama cross-coupling.

chloride (**2a**) and a screen of chiral ligands was conducted (see foot of Table 1). From an initial ligand library, we found that TADDOL phosphoramidites exhibited the highest enantioselectivity, in particular the ligand **L1**. All other well-known phosphoramidites (**L8–L9**) showed poor enantioselectivities.^[11b] We believe that TADDOL phosphoramidites such as **L1–L7** may be responsible for an enhanced rate of reductive elimination.

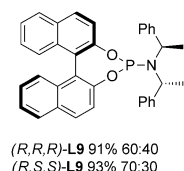
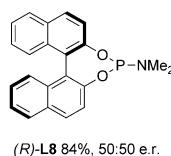
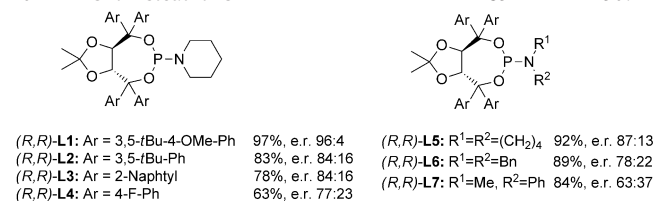
Alkylzinc halides ($RZnX$) are known to engage in a Schlenk equilibrium with their dialkylzinc counterparts (R_2Zn). The Fukuyama cross-coupling proceeds through a $RZnX$ species, while being ineffective for R_2Zn reagents.^[17] In the event, we observed that both the yield and enantioselectivity significantly improved upon addition of $ZnCl_2$ as an additive (Table 1). Not only does $ZnCl_2$ influence the Schlenk equilibrium in favor of $RZnX$, but it is also involved in accelerating the rate of racemization of secondary organozinc reagents, one of the crucial challenges named earlier.^[14a] In our system, the use of superstoichiometric amounts of $LiCl$, a common additive in Negishi cross-couplings,^[18] did not lead to any change in yield and enantioselectivity. Further screening identified MTBE as the optimal solvent and $Pd(OAc)_2$ as the best palladium catalyst. Additional reaction optimization by coupling of (1-phenylethyl)zinc bromide, instead of the organozinc chloride **2a**, provided the product in identical levels of enantioselectivity, albeit with decreased yield (entry 9). A change of the thioester moiety from aryl to alkyl afforded similar yields and enantioselectivities (entry 10), thus showing that the initial oxidative addition and the basicity/nucleophilicity of the resulting anionic sulfide released in solution are not crucial factors in this process.^[19]

With our optimized reaction conditions in hand, we explored the scope of secondary organozinc reagents (Table 2). Both *para*- and *meta*-methyl substituents were tolerated in the reaction. However, *ortho*-substituted organozinc reagents did not lead to any product formation. Chloride substituents were compatible with the reaction conditions and afforded products carrying an aryl halide, which can be used for additional modifications. Fluoride substituents could be employed in the reaction as well, however with slightly decreased enantioselectivity. Strong electron-withdrawing substituents like *para* CF_3 led to fast conversion and afforded

Table 1: Optimization of the reaction conditions.

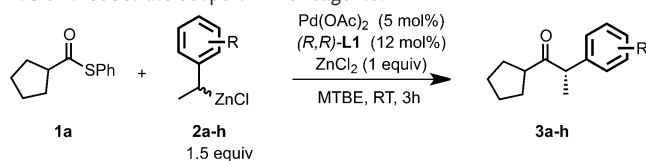


Entry ^[a]	Deviation from the standard conditions	Yield [%] ^[b]	e.r. ^[c]
1	none	97	96:4
2	no $ZnCl_2$	65	89:11
3	with 5 equivalent $LiCl$	95	95:5
4	THF instead of MTBE	94	75:25
5	toluene instead of MTBE	89	58:42
6	DCM instead of MTBE	72	84:16
7	$[Pd_2(dba)_3]$ instead of $Pd(OAc)_2$	98	94:6
8	$[Pd(allyl)Cl]_2$ instead of $Pd(OAc)_2$	93	90:10
9	(1-phenylethyl)zinc bromide instead of 2a	56	96:4
10	SEt instead of SPh	89	96:4



[a] Reactions conducted on a 0.1 mmol scale under argon atmosphere
 [b] Yield determined by 1H NMR analysis (internal standard). [c] The e.r. values were determined by chiral-phase GC analysis. dba = dibenzylidene acetone, DCM = dichloromethane, MTBE = methyl *tert*-butyl ether, THF = tetrahydrofuran.

Table 2: Substrate scope of zinc reagents.

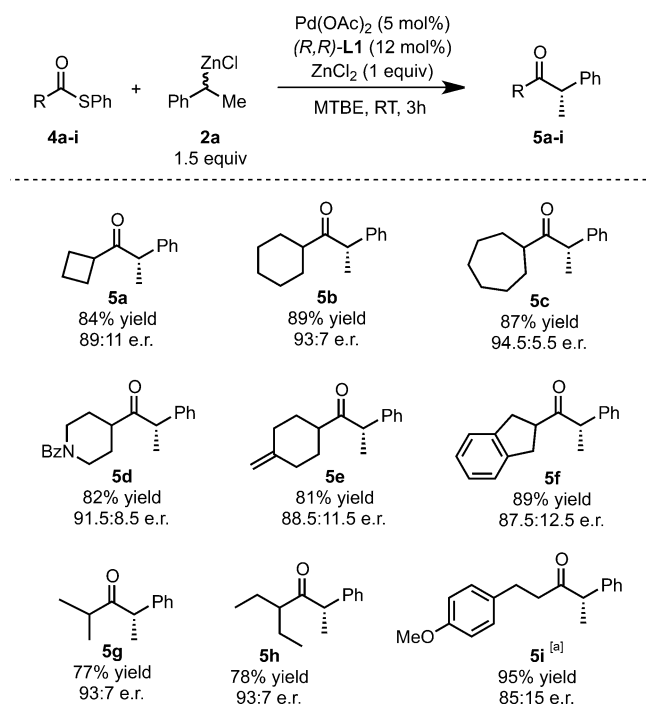


Entry ^[a]	R	Product	Yield [%] ^[b]	e.r. ^[c]
1	H	3a	90	96:4
2	4-Me	3b	88	88.5:11.5
3	3-Me	3c	85	91.5:8.5
4	3,5-Me	3d	78	88.5:11.5
5	4-Cl	3e	81	93:7
6	3-Cl	3f	83	87:13
7	3-F	3g	74	83.5:16.5
8	4- CF_3	3h	75	93.5:6.5

[a] Reactions conducted on a 0.1 mmol scale under argon atmosphere
 [b] Yield of isolated product. [c] The e.r. values were determined by either chiral-phase GC or HPLC analysis.

the desired ketone product in good yield and an enantiomeric ratio of 93.5:6.5 (entry 8).

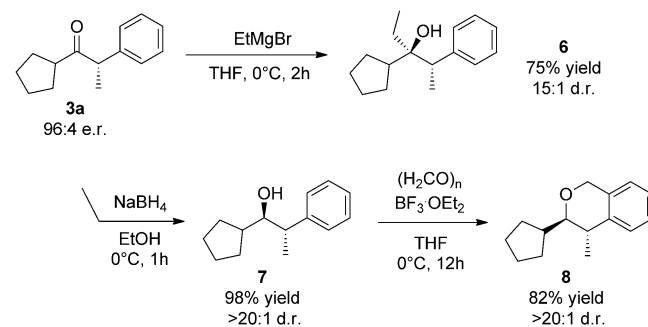
The scope of the thioester coupling partner was also investigated (Scheme 3). Varying the ring size gave good yields and enantioselectivities. Benzoyl-protected piperidine rings were tolerated under the reaction conditions as well as terminal alkenes. Furthermore, noncyclic substrates such as **4g,h** gave good conversions and enantiomeric ratios of 93:7. Linear substrates such as **4i** could also be applied in this reaction, although lower enantioselectivities were observed.



Scheme 3. Substrate scope with respect to the thioesters. All the reported yields and e.r. values refer to pure isolated material (see the Supporting Information for details)^[13,20] [a] Reaction was performed in the presence of 4 equivalents of LiCl. Bz = benzoyl.

We were then interested in exploring the potential for catalyst control in this chemistry, and were drawn to drug-derived thioesters, bearing an α -carbonyl chiral center, as substrates for this type of stereoselective cross-coupling (Table 3). For instance, the thioester **4j**, derived from the COX-inhibitor Naproxen, undergoes Fukuyama cross-coupling with the racemic organozinc reagent **2a** using PCy_3 as a ligand to deliver a mixture of both *anti*-**5j** and *syn*-**5j** diastereomers in a nearly 1:1 ratio. Strikingly, switching to $(R,R)\text{-L1}$ delivers the *anti* stereoisomer selectively (8:1 d.r.) with its antipode $(S,S)\text{-L1}$ affording clean access to the *syn* counterpart (7:1 d.r.). A similar outcome is observed with the Roche ester-derived substrate **4k**, the cross-coupling of which is similarly amenable to catalyst control. The configurational stability of two potentially labile benzylic stereogenic centers α to carbonyl groups in this transformation testifies to the mildness of the reaction conditions employed.

The enantioenriched α -disubstituted ketones reported herein can be further exploited in different synthetic transformations (Scheme 4). For example, diastereoselective Grignard addition could be achieved with EtMgBr to afford the tertiary alcohol in good yield and high diastereoselectivity. Similarly, diastereoselective reduction was achieved with NaBH_4 gave alcohol **7**. Treating this alcohol with paraformaldehyde and $\text{BF}_3\cdot\text{OEt}_2$ provides access to 3,4-disubstituted



Scheme 4. Elaboration of selected ketone products.

Table 3: Diastereoselective Fukuyama cross-coupling of α -chiral thioesters.^[a]

Substrates	With $(R,R)\text{-L1}$	With $(S,S)\text{-L1}$
 (<i>R</i>)-Naproxen thioester (4j)	 <i>anti</i> - 5j , 80% yield, 8:1 d.r.	 <i>syn</i> - 5j , 71% yield, 7:1 d.r.
 (<i>S</i>)- β -BnO-isobutyric thioester (4k)	 <i>syn</i> - 5k , 85% yield, 8:1 d.r.	 <i>anti</i> - 5k , 72% yield, 8:1 d.r.

[a] Reactions conducted on a 0.1 mmol scale under argon atmosphere. All the reported yields refer to pure isolated material. The d.r. values were determined by ^1H NMR analysis of the crude reaction mixture. Bn = Benzyl.

isochromane **8** in good yield and excellent diastereoselectivity.^[21]

In conclusion, we have developed the first general catalytic asymmetric method for the cross-coupling of thioesters by deracemization of racemic benzylic secondary organozinc reagents. This stereoconvergent process takes place under mild reaction conditions and allows the smooth preparation of enantioenriched acyclic α -disubstituted carbonyl compounds carrying potentially labile tertiary stereocenters. The development of further enantioconvergent cross-coupling reactions of broad synthetic utility is currently underway and shall be reported in due course.

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- [1] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; *Angew. Chem.* **2012**, *124*, 5150–5174.
- [2] R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492.
- [3] a) F. Lovering, *MedChemComm* **2013**, *4*, 515–519; b) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
- [4] For initial reports, see: a) C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595; b) F. O. Arp, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483.
- [5] For an overview, see: B. W. Glasspoole, C. M. Crudden, *Nat. Chem.* **2011**, *3*, 912–913.
- [6] Selected examples: a) T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nat. Chem.* **2010**, *2*, 125–130; b) S. Seel, T. Thaler, K. Takatsu, C. Zhang, H. Zipse, B. F. Straub, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2011**, *133*, 4774–4777; c) T. Thaler, L.-N. Guo, P. Mayer, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 2174–2177; *Angew. Chem.* **2011**, *123*, 2222–2225.
- [7] A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587–9652.
- [8] C. J. Cordier, R. J. Lundgren, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 10946–10949.
- [9] For studies on configurational stabilities of organometallic reagents, see: a) G. Whitesides, M. Witanowski, J. D. Roberts, *J. Am. Chem. Soc.* **1965**, *87*, 2854–2862; b) M. Witanowski, J. D. Roberts, *J. Am. Chem. Soc.* **1966**, *88*, 737–741; c) A. Guijarro, R. D. Rieke, *Angew. Chem. Int. Ed.* **2000**, *39*, 1475–1479; *Angew. Chem.* **2000**, *112*, 1535–1539.
- [10] For pioneering examples of deracemization of chiral secondary alkylmagnesium and alkylzinc reagents with limited scope, see: a) T. Hayashi, M. Tajika, K. Tamao, M. Kumada, *J. Am. Chem. Soc.* **1976**, *98*, 3718–3719; b) T. Hayashi, M. Fukushima, M. Konishi, M. Kumada, *Tetrahedron Lett.* **1980**, *21*, 79–82; c) T. Hayashi, A. Yamamoto, M. Hojo, Y. Ito, *J. Chem. Soc. Chem. Commun.* **1989**, 495–496; d) M. Lemaire, J. Buter, B. K. Vriesema, R. M. Kellogg, *J. Chem. Soc. Chem. Commun.* **1984**, 308–309; e) J. H. Griffin, R. M. Kellogg, *J. Org. Chem.* **1985**, *50*, 3261–3266; f) G. A. Cross, R. M. Kellogg, *J. Chem. Soc. Chem. Commun.* **1987**, 1744–1746; g) G. Cross, B. K. Vriesema, G. Boven, R. M. Kellogg, F. van Bolhuis, *J. Organomet. Chem.* **1989**, *370*, 357–381.
- [11] a) T. Fukuyama, H. Tokuyama, S. Yokoshima, T. Yamashita, *Tetrahedron Lett.* **1998**, *39*, 3189–3192; b) A. H. Cherney, S. E. Reisman, *Tetrahedron* **2014**, *70*, 3259–3265.
- [12] Catalytic asymmetric synthesis of acyclic α -disubstituted ketones: a) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181; b) X.-X. Yan, C.-G. Liang, Y. Zhang, W. Hong, B.-X. Cao, L.-X. Dai, X.-L. Hou, *Angew. Chem. Int. Ed.* **2005**, *44*, 6544–6546; *Angew. Chem.* **2005**, *117*, 6702–6704; c) W.-H. Zheng, B.-H. Zheng, Y. Zhang, X.-L. Hou, *J. Am. Chem. Soc.* **2007**, *129*, 7718–7719; d) P. M. Lundin, J. Esquivias, G. C. Fu, *Angew. Chem. Int. Ed.* **2009**, *48*, 154–156; *Angew. Chem.* **2009**, *121*, 160–162; e) S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 5010–5011.
- [13] A. H. Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 7442–7445.
- [14] a) C. Darcel, F. Flachsman, P. Knochel, *Chem. Commun.* **1998**, 205–206; b) A. Boudier, C. Darcel, F. Flachsman, L. Micouin, M. Oestreich, P. Knochel, *Chem. Eur. J.* **2000**, *6*, 2748–2761.
- [15] S. Klein, I. Marek, J.-F. Normant, *J. Org. Chem.* **1994**, *59*, 2925–2926.
- [16] a) L. Li, S. Zhao, A. Joshi-Pangu, M. Diane, M. R. Biscoe, *J. Am. Chem. Soc.* **2014**, *136*, 14027–14030; b) M. Pompeo, R. D. J. Froese, N. Hadei, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 11354–11357; *Angew. Chem.* **2012**, *124*, 11516–11519.
- [17] Y. Mori, M. Seki, *Adv. Synth. Catal.* **2007**, *349*, 2027–2038.
- [18] K. Böck, J. E. Feil, K. Karaghiosoff, K. Koszinowski, *Chem. Eur. J.* **2015**, *21*, 5548–5560.
- [19] Samples of product formed at intermediate conversions had constant levels of enantiopurity, thus demonstrating that an effective DKR takes place.
- [20] S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266.
- [21] a) J. Ralph, J. Peng, F. Lu, *Tetrahedron Lett.* **1998**, *39*, 4963; b) Y. Rusman, B. W. Held, R. A. Blanchette, S. Wittlin, C. E. Salomon, *J. Nat. Prod.* **2015**, *78*, 1456–1460.

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