Nickel/Photoredox-Catalyzed Asymmetric Reductive Cross-Coupling of Racemic α-Chloro Esters with Aryl Iodides

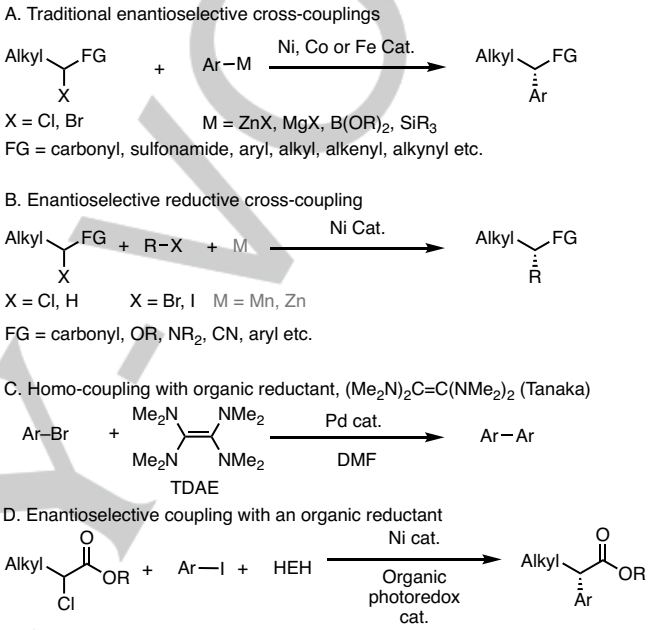
Haixing Guan, [a] Qianwen Zhang, [a] Patrick J. Walsh*[b] and Jianyou Mao*[a]

Abstract: A unique nickel/organic photoredox co-catalyzed asymmetric reductive cross-coupling between α-chloro esters and aryl iodides is advanced. This cross-electrophile coupling reaction employs an organic reductant (Hantzsch ester), whereas most reductive cross-coupling reactions use stoichiometric metals. A diverse array of valuable α-aryl esters is formed under these conditions with high enantioselectivities (up to 94%) and good yields (up to 88%). α-Aryl esters represent an important family of nonsteroidal anti-inflammatory drugs. This novel synergistic strategy expands the scope of Ni-catalyzed reductive asymmetric cross-coupling reactions.

Introduction

The catalytic enantioselective construction of C−C bonds remains one of the foremost challenges in organic synthesis.[1] Two general approaches to transition-metal-catalyzed asymmetric C(sp^2)−C(sp^3) bond-forming reactions have been developed. The first class is the conventional transition metal-catalyzed enantioselective cross-coupling reactions, such as the Kumada[2], Negishi[3], Suzuki−Miyaura[4], and Hiyama,[5] primarily driven by Fu and co-workers (Scheme 1A).

The second class of enantioselective coupling reactions involves reductive cross-couplings, which couple two electrophiles using stoichiometric reductants to turn over the catalysts. The advantage of this latter approach is that it avoids the synthesis of reactive and air-sensitive organometallic cross-coupling partners. To date, an array of reductive cross-coupling reactions has been described, mostly using stoichiometric metal reducing agents.[6] More recently, elegant asymmetric reductive cross-coupling processes have been disclosed using manganese[7] or zinc[8] as the terminal reductant (Scheme 1B). These reactions, however, are complicated by the need to dispose of the stoichiometric metal waste. A complementary approach to metal promoted reductive coupling reactions employs organic reducing agents. A pioneering study by Tanaka and coworkers[9] with tetrakis(dimethylamino)ethylene (TDAE) as reductant led to the homo-coupling of aryl halides to make symmetrical biaryls (Scheme 1C). Inspired by this advance, Weix's team demonstrated that TDAE could supply electrons for cross-electrophile coupling reactions,[10] and Reisman's group reported an enantioselective coupling of *N*-hydroxyphthalimide esters with vinyl bromides.[7f] Other organic reducing agents recently used include amines, Hantzsch ester (HEH) and $(Et_3Si)_3Si–H$.[11]



Scheme 1. Transition-Metal-Catalyzed Asymmetric Coupling Reaction

To develop cross-electrophile coupling reactions with organic reducing agents we turned to photoredox methods.[12] Dual photoredox/transition metal catalysis has gained traction in enantioselective construction of C−C bonds,[13] however, we are unaware of its use in enantioselective dual catalysis cross-electrophile coupling reactions. Herein, we employ an organic photoredox catalyst with Hantzsch ester (HEH) as the terminal organic reductant to realize the nickel catalyzed asymmetric reductive cross-coupling of α-chloro esters with aryl iodides to furnish α-aryl esters (Scheme 1D). This method represents an advance over prior methods that employed prefunctionalized aryl coupling partners (organosilane, Grignard or organozinc reagents),[14] or preformed enolates.[15] It is also an alternative strategy for the enantioselective formation of C(sp^2)−C(sp^3) bonds to the use of stoichiometric metal as reductant. The α-aryl esters prepared herein belong to an important class of nonsteroidal anti-inflammatory drugs (NSAIDs).[16]

Results and Discussion

We began our investigation into the reductive coupling between α-chloro ester (**1a**) and iodobenzene (**2a**) (for a systematic study of reaction conditions screened see Table S1 in the Supporting

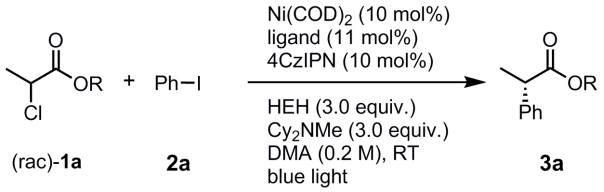
[a] H. Guan, Q. Zhang, Prof. Dr. J. Mao
Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, 30 South Puzhu Road, Nanjing 211816 (P.R. China)
E-mail: ias_jymao@njtech.edu.cn
[b] Prof. Dr. P. J. Walsh
Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, PA 19104, USA
E-mail: pwalsh@sas.upenn.edu

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

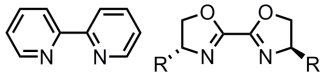
Information). Initially, the racemic reaction was optimized using α-chloro ester (**1a**) with iodobenzene (**2a**), $Ni(COD)_2$ (10 mol%, COD = 1,5-cyclooctadiene), 4,4'-dimethoxy-2,2'-bipyridine (11 mol%), $[Ir(ppy)_2(dtb\text{-}bipy)]^+[PF_6]^-$ (10 mol%), and Cy_2NMe as the reducing agent and irradiation with blue LEDs, giving 82% AY (Table S1). These conditions, however, did not translate well with enantioenriched ligands, so the system was reoptimized. The reoptimized conditions for the *racemic* coupling of α-chloro ester (**1a**) with iodobenzene (**2a**) involved irradiation with blue LEDs of an *N,N*-dimethylacetamide (DMA) solution of $Ni(COD)_2$ (10 mol%), bipyridine (Bipy, 11 mol%), Hantzsch ester (3 equiv), photoredox catalyst 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN, 10 mol%) and *N,N*-dicyclohexylmethylamine (Cy_2NMe, 3 equiv) at room temperature for 48 h. Under these conditions, the assay yield (AY) for the racemic product **3a** was 85% (Table 1, entry 1, determined by GC using tetradecane as an internal standard). We next initiated a search for an enantioselective catalyst. Several chiral ligands such as bioxazolines[7a, 7f, 17] including **L6** and phosphino-oxazoline ligands[7c], have emerged as generally useful ligand for asymmetric cross electrophile coupling reactions. Based on these prior studies, we tested several classes of enantioenriched ligands (see Supporting Information for details), and found that the bioxazoline (BiOX) framework was also promising in our reaction. With R = *n*-Pr, the product was obtained in 22% ee and 23% AY (entry 2). Bulkier ligands with R = *i*-Pr (**L2**, 21% AY, 68% ee, entry 3) and *i*-Bu (**L3**, 21% AY, 24% ee, entry 4) indicated that a secondary alkyl group was better than a primary one. **L4** and **L5**, containing *sec*-Bu and *t*-Bu groups, provided product in 25% AY and 64% ee and 35% AY with only 5% ee, respectively (entries 5–6). These results inspired the synthesis of the known 4-heptyl substituted ligand **L6**,[7e, 7g] which gave 74% ee (24% AY, entry 7).

Inspired by the work of Nakamura,[2c] we next opted to modify the ester OR group. Continuing with **L6**, we examined OR = OMe or OEt. The enantioselectivities were 75 and 79%, respectively (entries 8 and 9). The *t*-Bu ester only resulted in a small increase to 80% ee (entry 10). In contrast, increasing the steric bulk of the ester OR substituent to 2,3,3-trimethylbut-2-yl, the product was produced with 90% ee (entry 11), albeit in 50% AY. We next turned our attention to improving the yield of **3a**. By increasing the ratio of **1a** to **2a** from 1:1 to 1:2 and 1:3, the AY increased to 82% (entries 11–13). Ultimately the product **3a** was isolated by column chromatography in 77% yield. Control experiments confirmed that little product was formed in the absence of Ni precursor, **L6**, blue LEDs, Cy_2NMe or 4CzIPN. HEH was crucial for high yields, as only 21% yield of **3a** was detected without HEH (entry 14). In this control experiment, however, the enantioselectivity remained 90%, suggesting that the HEH is not involved in the enantiodetermining step, but is essential for catalyst turnover.

Table 1. Optimization of reaction conditions.[a]



Entry	**1a**:**2a**	Ligand	R	AY (%)[b]	*ee* (%)[c]
1	1:1	Bipy	Bn	85	--
2	1:1	**L1**	Bn	23	22
3	1:1	**L2**	Bn	21	68
4	1:1	**L3**	Bn	21	24
5	1:1	**L4**	Bn	25	64
6	1:1	**L5**	Bn	35	5
7	1:1	**L6**	Bn	24	74
8	1:3	**L6**	Me	76[d]	75
9	1:3	**L6**	Et	82[d]	79
10	1:3	**L6**	*t*-Bu	85[d]	80
11	1:1	**L6**	2,3,3-trimethylbut-2-yl	50	90
12	1:2	**L6**	2,3,3-trimethylbut-2-yl	65	90
13	1:3	**L6**	2,3,3-trimethylbut-2-yl	82(77[d])	90
14[e]	1:3	**L6**	2,3,3-trimethylbut-2-yl	21	90



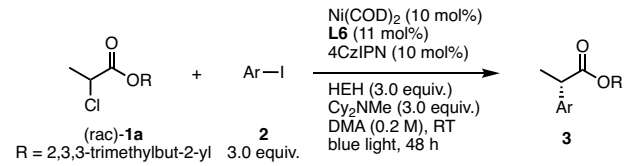
L1, R = *n*-Pr **L4**, R = *s*-Bu
L2, R = *i*-Pr **L5**, R = *t*-Bu
L3, R = *i*-Bu **L6**, R = 4-Hep

[a] Reactions conducted under Ar on 0.1 mmol scale for 48 h. [b] Determined by GC using tetradecane as an internal standard. [c] Determined by chiral HPLC on a CHIRALPAK IC−3 column. [d] Isolated yield. [e] No HEH.

With the optimized reaction conditions in hand, we next focused on the scope of the aryl iodide coupling partners using α-chloro ester **2a** (Scheme 2). Aryl iodides with alkyl groups in the 4-position (Me, *t*-Bu) and 3-position (Me) all exhibited 90% ee and good yields (69–75%, **3b**, **3c**, **3n**). The (*S*) configuration of **3a** was assigned by comparison of the optical rotation with the literature value while the (*S*) configuration of **3c** was confirmed by reduction to the alcohol and comparison of its HPLC retention time on the chiral column with the literature values (see Supporting Information for details). Sterically hindered 2-iodo toluene resulted in slightly diminished ee (86%, 58% yield). Iodobenzenes substituted by electron-donating (4-NMe_2, 4-OMe) were formed in 84–86% ee with 52–72% yields (**3d**–**3e**). Aryl iodides with electronegative or electron withdrawing groups (4-F, 4-CF_3, 4-Cl, 3-Cl, 4-Ac, 4-CO_2Et, 4-CN, 3-OPh) exhibited high enantioselectivities (86–91%). It is noteworthy that the boronate ester was also well-tolerated, affording the product **3m** in 75% yield with 90% ee. 4-Iodo biphenyl derivatives were fine substrates, furnishing the products **3r** and **3s** with 88–89% ee and 85–86% yield. Likewise, 1-(4-iodophenyl)-1*H*-pyrrole and 2-iodo-9*H*-fluorene underwent coupling in 73–75% yield with enantioselectivities of 88–89%. Aryl iodides with extended π-systems, such as those derived from 2-iodo-6-methyoxynaphthylene and 1-iodonaphthylene provided products **3v** (52% yield, 87% ee) and **3w** (49% yield, 69% ee). Heterocycles are important structural motifs in medicinal chemistry. Several heteroaryl iodides were, therefore, examined. 5-Iodo-1-methyl indole, 2-fluoro-5-iodopyridine, 3-iodo thiophene and 3-iodobenzofuran all exhibited good enantioselectivities (84–89%), with yields ranging from 47–60%. For a method to be useful, it must be practical and scalable. When the reaction was

conducted on 1.0 mmol, **3r** was produced in 88% yield with 89% ee. After isolation by column chromatography, 4CzIPN can be reused without any change in activity (for at least two cycles).

Scheme 2. Scope of aryl and (hetero)aryl iodides.[a]



R' = H **3a**, 77%, 90% ee
= Me **3b**, 75%, 90% ee
= t-Bu **3c**, 69%, 90% ee
= NMe_2 **3d**[b], 72%, 84% ee
= OMe **3e**[b], 52%, 86% ee
= OCF_3 **3f**[b], 72%, 86% ee
= F **3g**, 72%, 90% ee
= CF_3 **3h**, 69%, 87% ee
= Cl **3i**[c], 70%, 86% ee
= Ac **3j**, 70%, 90% ee
= CO_2Et **3k**, 72%, 91% ee
= CN **3l**, 73%, 89% ee
= Bpin **3m**, 75%, 90% ee

R' = Me, **3n**[b], 70%, 90% ee
= OPh, **3o**, 71%, 90% ee
= Cl, **3p**, 73%, 90% ee

3q, 58%, 86% ee

3r, 86%, 89% ee
88%, 89% ee[d]

3s, 85%, 88% ee

3t, 73%, 88% ee

3u, 75%, 89% ee

3v, 52%, 87% ee

3w, 49%, 69% ee

3x, 60%, 89% ee

3y, 60%, 88% ee

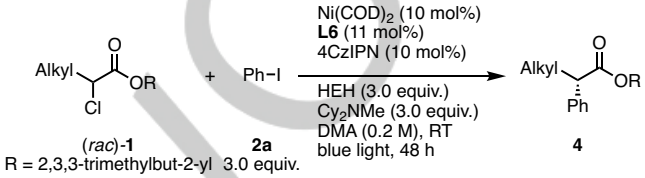
3z, 47%, 84% ee

3za, 52%, 89% ee

[a] All reactions conducted under Ar on 0.1 mmol scale. Yield is that of the isolated product. The *ee* values were determined by chiral-phase HPLC. [b] The reactions were run for 96 h. [c] The reactions were run for 72 h. [d] Conducted on 1.0 mmol scale.

We next examined the scope of the α-alkyl group of the α-chloro esters (Scheme 3). We were please to find that not only primary alkyl groups, such as Et (**4a**), *n*-Bu (**4b**) and *i*-Bu (**4c**), but also secondary alkyl groups, including isopropyl (**4d**) and cyclopentyl (**4e**), exhibited good yields (77–82%) and excellent enantioselectivities (91–94%). In prior publications, secondary alkyl esters either gave low enantioselectivities or were not included among the reported substrates.[2b, 2c, 5a] Alkyl groups bearing aryl substituents (**4f**–**4i**) were also tolerated and the corresponding coupling products were isolated in 58–83% yield with enantioselectivities of 87–89%. Although a β-OMe did not impact the reaction yield (85%), diminished enantioselectivity was observed (54%). When the methoxy group was located at the δ-position, however, it did not negatively impact the enantioselectivity (90% ee, 73% yield). It should be noted that only traces of product **4l** was obtained, with most of the starting ester recovered as dechlorination byproduct **4l'** (65%, see Supporting Information for details).

Scheme 3. Scope of α-chloro esters.[a]



4a, 82%, 93% ee

4b, 81%, 93% ee

4c, 79%, 94% ee

4d, 80%, 93% ee

4e, 77%, 91% ee

4f, 72%, 89% ee

4g, 58%, 89% ee

4h, 83%, 87% ee

4i, 71%, 87% ee

4j, 85%, 54% ee

4k, 73%, 90% ee

4l, trace

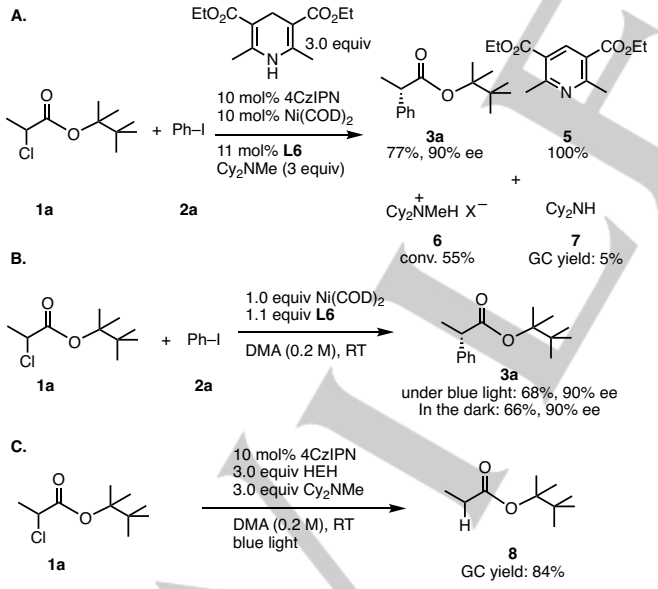
[a] All reactions conducted under Ar on 0.1 mmol scale. Yield is that of the isolated product. The *ee* values were determined by chiral-phase HPLC.

To gain insight into the mechanism of this reductive cross-coupling reaction, additional experiments were performed. Both the HEH and tertiary amines are known to behave as sacrificial reducing agents. Therefore, we set out to understand the role of these reagents in the reductive arylation. Conducting the reaction of **1a** and **2a** under the standard conditions with 3 equiv HEH and 3 equiv Cy_2NMe (Scheme 4A), the product **3a** was isolated in 77% yield with 90% ee. The fate of the HEH was the expected pyridine (isolated in 100% yield relative to HEH), derived from donation of 2 electrons and two protons. The Cy_2NMe largely acted as a base in the reaction, as determined by the isolation of 55% of the total Cy_2NMe as Cy_2NMe•HX (**6**, see supporting information for details).[17] Only about 5% of the demethylated product, Cy_2NH, was detected after workup. The demethylated amine likely arises from oxidation of the amine by *4CzIPN to the amine radical cation, loss of H• to generate the iminium ion, and hydrolysis by advantageous water during the

reaction or upon workup.[18] These results indicate that HEH is the terminal reductant for the reaction.

In addition to the role of the Ni catalyst in cleavage of the Ar–I bond through oxidative addition, we considered the possibility that Ni could act as a catalytic reductant[19] toward the α-chloro ester. Stoichiometric studies with *1.0 equiv* $Ni(COD)_2$ and 1.1 equiv **L6** under blue light irradiation and in the absence of HEH and Cy_2NMe, established that **1a** reacted with **2a** to form cross-coupled product **3a** (68% yield, 90% ee) (Scheme 4B). Likewise, when this reaction was conducted without irradiation, cross-coupled product **3a** (66% yield, 90% ee) (Scheme 4B). It is noteworthy that the ee of these stoichiometric reactions are identical to that observed under the standard catalytic conditions (Table 1, entry 13). This observation suggests that the enantiodetermining step in the catalytic and stoichiometric reactions (Scheme 4B) are identical, and do not involve the HEH or Cy_2NMe.

It is interesting to note that organic photoredox catalysts are also reported to reduce α-halo esters to dehalogenated esters in the presence of HEH as the hydrogen atom donor.[20] We performed the model reaction without Ni/**L6** and iodobenzene (Scheme 4C). The dehalogenated product (**8**) can be obtained in 84% AY. In this experiment it is proposed that the photoredox catalyst undergoes SET to the α-halo carbonyl compounds to generate α-carbonyl radicals. Abstraction of H• from HEH by α-carbonyl radicals generates the dehalogenated products. Given that our system also proceeds via an α-carbonyl radical, it must be that the α-carbonyl radicals undergo addition to L*Ni(Ar)I faster than HAT from HEH.



Scheme 4. Mechanistic experiments.

Based on the mechanistic experiments above, and related studies in the literature,[21] a dual catalytic process for the asymmetric reductive cross-coupling appears reasonable (Figure 1). The (BiOX)Ni(0) species oxidatively adds the aryl iodide (**2**) to give the (BiOX)Ni(Ar)I complex.[6c] Next, the α-chloro ester (**1**) is reduced by SET to the α-carbonyl radical. There are three possibilities for this reduction. Based on Scheme 4B reduction could take place from Ni(0) (Figure 1) or Ni(I) (Figure S1A in the Supporting Information). Alternatively, the reduced photocatalyst 4CzIPN$^{\bullet-}$ may be responsible for the reduction (as described above[20]). The α-carbonyl radical species is quickly trapped by (BiOX)Ni(Ar)I to generate the reactive Ni(III) species. The resulting Ni(III) complex[22] then undergoes rapid reductive elimination to form the $C(sp^2)-C(sp^3)$ bond of **3a**. After excitation of 4CzIPN by blue light, the long lived photoexcited state *4CzIPN (τ = 5.1 ± 0.5 μs) can be reduced by HEH to give 4CzIPN$^{\bullet-}$ ($E1/2^{red}$ = −1.21 V vs SCE).[23] The $L_nNi^{(0)}$ species could be regenerated by SET [$E1/2^{red}$ (Ni^{II}/Ni^0) = −1.2 V vs SCE] from 4CzIPN$^{\bullet-}$.[21a]

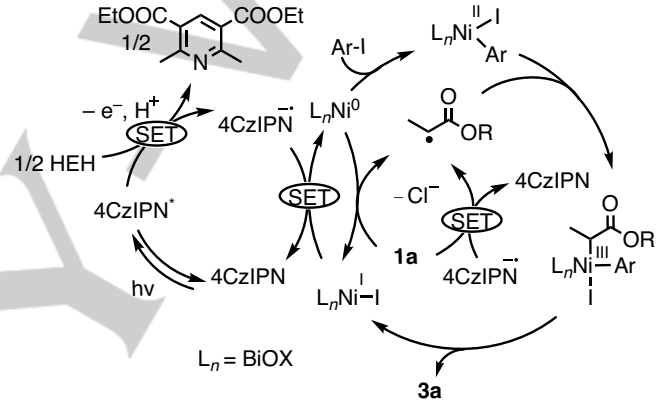


Figure 1. Plausible catalytic reaction pathway.

Conclusion

In summary, we have developed the first enantioselective dual nickel and organic photoredox catalyzed reductive cross-coupling between α-chloro esters and aryl iodides to afford α-aryl esters. Enantioenriched α-aryl ester derivatives are important precursors to nonsteroidal anti-inflammatory medications. Key features and advantages of this method include broad scope in both coupling partners, avoidance of preformed organometallic reagents, and circumvention of stoichiometric metal reductants used in most cross-electrophile coupling reactions. Future directions include the use of electrochemical methods as a source of electrons for enantioselective reductive coupling reactions.[24]

Acknowledgements

The authors acknowledge the National Natural Science Foundation of China (21801128 to J.M.), Natural Science Foundation of Jiangsu Province, China (BK20170965 to J.M) and Nanjing Tech University (3980001601 and 39837112) for

financial support. PJW thanks the Petroleum Research Fund (59570-ND1) and US National Science Foundation (CHE-1902509).

Keywords: asymmetric reductive α-arylation • cooperative catalysis • nickel • organic photosensitizer • carboxylic acids

[1] a) E. C. Swift, E. R. Jarvo, *Tetrahedron* **2013**, *69*, 5799-5817; b) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *Chem. Rev.* **2015**, *115*, 9587-9652; c) F. Wang, P. Chen, G. Liu, *Acc. Chem. Res.* **2018**, *51*, 2036-2046.

[2] a) S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 1264-1266; b) J. Mao, F. Liu, M. Wang, L. Wu, B. Zheng, S. Liu, J. Zhong, Q. Bian, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 17662-17668; c) M. Jin, L. Adak, M. Nakamura, *J. Am. Chem. Soc.* **2015**, *137*, 7128-7134; d) M. S. Eno, A. Lu, J. P. Morken, *J. Am. Chem. Soc.* **2016**, *138*, 7824-7827.

[3] a) C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594-4595; b) J. T. Binder, C. J. Cordier, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 17003-17006; c) H.-Q. Do, E. R. R. Chandrashekar, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 16288-16291; d) Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 5520-5524; e) Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2015**, *137*, 9523-9526; f) J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, *Science* **2016**, *354*, 1265-1269.

[4] a) M. C. Willis, L. H. W. Powell, C. K. Claverie, S. J. Watson, *Angew. Chem., Int. Ed.* **2004**, *43*, 1249-1251; b) B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 6694-6695; c) P. M. Lundin, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 11027-11029; d) A. S. Dudnik, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 10693-10697; e) H. Cong, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 3788-3791; f) G. Xu, W. Fu, G. Liu, C. H. Senanayake, W. Tang, *J. Am. Chem. Soc.* **2014**, *136*, 570-573; g) X. Jiang, M. Gandelman, *J. Am. Chem. Soc.* **2015**, *137*, 2542-2547; h) P. Schafer, T. Palacin, M. Sidera, S. P. Fletcher, *Nat. Commun.* **2017**, *8*, 15762pp.

[5] a) X. Dai, N. A. Strotman, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 3302-3303; b) J. Gonzalez, P. Schafer, S. P. Fletcher, *ChemRxiv, Catal.* **2018**, 1-4; c) A. Varenikov, M. Gandelman, *Nat. Commun.* **2018**, *9*, 3566.

[6] a) D. A. Everson, R. Shrestha, D. J. Weix, *J. Am. Chem. Soc.* **2010**, *132*, 920-921; b) X. Wang, S. Wang, W. Xue, H. Gong, *J. Am. Chem. Soc.* **2015**, *137*, 11562-11565; c) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767-1775; d) M. Borjesson, T. Moragas, D. Gallego, R. Martin, *ACS Catal.* **2016**, *6*, 6739-6749; e) X. Wang, Y. Dai, H. Gong, *Top. Curr. Chem.* **2016**, *374*, 1-29; f) T. Lin, J. Mi, L. Song, J. Gan, P. Luo, J. Mao, P. J. Walsh, *Org. Lett.* **2018**, *20*, 1191-1194; g) X. Wang, G. Ma, Y. Peng, C. E. Pitsch, B. J. Moll, T. D. Ly, X. Wang, H. Gong, *J. Am. Chem. Soc.* **2018**, *140*, 14490-14497.

[7] a) A. H. Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 7442-7445; b) A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2014**, *136*, 14365-14368; c) N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2015**, *137*, 10480-10483; d) Y. Zhao, D. J. Weix, *J. Am. Chem. Soc.* **2015**, *137*, 3237-3240; e) K. E. Poremba, N. T. Kadunce, N. Suzuki, A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2017**, *139*, 5684-5687; f) N. Suzuki, J. L. Hofstra, K. E. Poremba, S. E. Reisman, *Org. Lett.* **2017**, *19*, 2150-2153; g) B. P. Woods, M. Orlandi, C.-Y. Huang, M. S. Sigman, A. G. Doyle, *J. Am. Chem. Soc.* **2017**, *139*, 5688-5691; h) Z.-X. Tian, J.-B. Qiao, G.-L. Xu, X. Pang, L. Qi, W.-Y. Ma, Z.-Z. Zhao, J. Duan, Y.-F. Du, P. Su, X.-Y. Liu, X.-Z. Shu, *J. Am. Chem. Soc.* **2019**, *141*, 7637-7643; i) J. L. Hofstra, A. H. Cherney, C. M. Ordner, S. E. Reisman, *J. Am. Chem. Soc.* **2018**, *140*, 139-142.

[8] a) K. Wang, Z. Ding, Z. Zhou, W. Kong, *J. Am. Chem. Soc.* **2018**, *140*, 12364-12368; b) Y. Jin, C. Wang, *Angew. Chem., Int. Ed.* **2019**, *58*, 6722-6726; c) D. Anthony, Q. Lin, J. Baudet, T. Diao, *Angew. Chem., Int. Ed.* **2019**, *58*, 3198-3202.

[9] a) M. Kuroboshi, Y. Waki, H. Tanaka, *Synlett* **2002**, *2002*, 0637-0639; b) M. Kuroboshi, Y. Waki, H. Tanaka, *J. Org. Chem.* **2003**, *68*, 3938-3942.

[10] a) D. A. Everson, B. A. Jones, D. J. Weix, *J. Am. Chem. Soc.* **2012**, *134*, 6146-6159; b) D. A. Everson, R. Shrestha, D. J. Weix, *J. Am. Chem. Soc.* **2010**, *132*, 920-921; c) L. L. Anka-Lufford, K. M. M. Huihui, N. J. Gower, L. K. G. Ackerman, D. J. Weix, *Chem. Eur. J.* **2016**, *22*, 11564-11567.

[11] a) K. Shimomaki, K. Murata, R. Martin, N. Iwasawa, *J. Am. Chem. Soc.* **2017**, *139*, 9467-9470; b) Q.-Y. Meng, S. Wang, B. König, *Angew. Chem., Int. Ed.* **2017**, *56*, 13426-13430; c) T. Q. Chen, D. W. C. MacMillan, *Angew. Chem., Int. Ed.* **2019**, 58, 14584–14588; d) J. Yi, S. O. Badir, L. M. Kammer, M. Ribagorda, G. A. Molander, *Org. Lett.* **2019**, *21*, 3346-3351.

[12] a) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035-10074; b) J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy, N. R. Patel, G. A. Molander, *Acc. Chem. Res.* **2016**, *49*, 1429-1439; c) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nat. Rev. Chem.* **2017**, *1*, 0052.

[13] a) J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433-436; b) O. Gutierrez, J. C. Tellis, D. N. Primer, G. A. Molander, M. C. Kozlowski, *J. Am. Chem. Soc.* **2015**, *137*, 4896-4899; c) Z. Zuo, H. Cong, W. Li, J. Choi, G. C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832-1835; d) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075-10166; e) W. Ding, L.-Q. Lu, Q.-Q. Zhou, Y. Wei, J.-R. Chen, W.-J. Xiao, *J. Am. Chem. Soc.* **2017**, *139*, 63-66; f) H.-H. Zhang, J.-J. Zhao, S. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 16914-16919; g) F.-D. Lu, D. Liu, L. Zhu, L.-Q. Lu, Q. Yang, Q.-Q. Zhou, Y. Wei, Y. Lan, W.-J. Xiao, *J. Am. Chem. Soc.* **2019**, *141*, 6167-6172.

[14] a) J. Mao, F. Liu, M. Wang, L. Wu, B. Zheng, S. Liu, J. Zhong, Q. Bian, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 17662-17668; b) F. Liu, J. Zhong, Y. Zhou, Z. Gao, P. J. Walsh, X. Wang, S. Ma, S. Hou, S. Liu, M. Wang, M. Wang, Q. Bian, *Chem. Eur. J.* **2018**, *24*, 2059 – 2064; c) X. Dai, N. A. Strotman, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 3302-3303.

[15] Z. Huang, Z. Liu, J. Zhou, *J. Am. Chem. Soc.* **2011**, *133*, 15882-15885.

[16] a) M. F. Landoni, A. Soraci, *Curr. Drug Metab.* **2001**, *2*, 37-51; b) H. Dhall, A. Kumar, A. K. Mishra, *Curr. Bioact. Compds.* **2018**, *14*, 26-32.

[17] R. Wang, M. Ma, X. Gong, G. B. Panetti, X. Fan, P. J. Walsh, *Org. Lett.* **2018**, *20*, 2433-2436.

[18] a) L.-L. Liao, G.-M. Cao, J.-H. Ye, G.-Q. Sun, W.-J. Zhou, Y.-Y. Gui, S.-S. Yan, G. Shen, D.-G. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 17338-17342; b) X. Fan, X. Gong, M. Ma, R. Wang, P. Walsh, J., *Nat. Commun.* **2018**, *9*, 4936.

[19] a) S. Biswas, D. J. Weix, *J. Am. Chem. Soc.* **2013**, *135*, 16192-16197; b) A. C. Wotal, R. D. Ribson, D. J. Weix, *Organometallics* **2014**, *33*, 5874-5881.

[20] M. Neumann, S. Fueldner, B. Koenig, K. Zeitler, *Angew. Chem., Int. Ed.* **2011**, *50*, 951-954.

[21] a) Q.-Y. Meng, S. Wang, G. S. Huff, B. Koenig, *J. Am. Chem. Soc.* **2018**, *140*, 3198-3201; b) J. Luo, J. Zhang, *ACS Catal.* **2016**, *6*, 873-877.

[22] G. C. Fu, *ACS Cent. Sci.* **2017**, *3*, 692-700.

[23] H. Uoyama, K. Goushi, K. Shizu, H. Nomura, C. Adachi, *Nature* **2012**, *492*, 234-238.

[24] M. Durandetti, J. Périchon, J.-Y. Nédélec, *J. Org. Chem.* **1997**, *62*, 7914-7915.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

RESEARCH ARTICLE

Text for Table of Contents

((Insert TOC Graphic here))

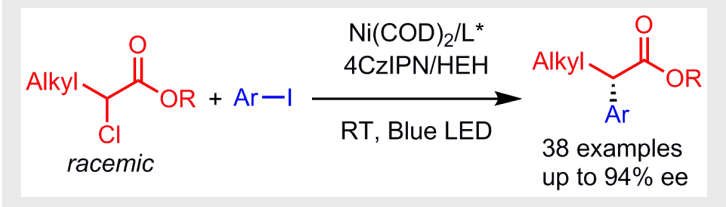
*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Layout 2:

RESEARCH ARTICLE



Text for Table of Contents

Haixing Guan, Qianwen Zhang, Patrick J. Walsh, and Jianyou Mao**

Page No. – Page No.

Nickel/Photoredox-Catalyzed Asymmetric Reductive Cross-Coupling of Racemic α-Chloro Esters with Aryl Iodides

The first dual nickel/photoredox catalyzed asymmetric reductive cross-coupling was developed. Three advantages of this reaction include: 1) no preformed nucleophiles; 2) no metal reductant; and 3) excellent scope.