Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b02120 • Publication Date (Web): 03 Jul 2016

Ni-Catalyzed Enantioselective *C*-Acylation of α-Substituted Lactams

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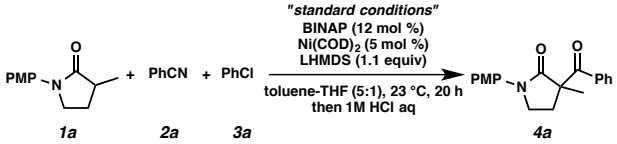
Supporting Information Placeholder

ABSTRACT: A new strategy for the catalytic enantioselective *C*-acylation to generate α-quaternary substituted lactams is reported. Ni-catalyzed three-component coupling of lactam enolates, benzonitriles, and aryl halides produce β-imino lactams that then afford β-keto lactams by acid hydrolysis. Use of a readily available Mandyphos-type ligand and the addition of LiBr enables the construction of quaternary stereocenters on α-substituted lactams to form β-keto lactams in up to 94% ee.

The catalytic enantioselective construction of quaternary stereocenters remains a challenging problem in synthetic chemistry.[1,2] Catalytic enantioselective reactions of enolates with electrophiles are among the most useful processes to construct quaternary stereocenters.[3] In this area, remarkable success has been achieved in the context of reactions such as enantioselective alkylations, conjugate additions, arylations, and aldol reactions.[1b,c,d] By contrast, there remains a paucity of enantioselective *C*-acylation reactions of enolates that enable access to β-keto carbonyl compounds. Recently, intramolecular acyl transfer strategies such as asymmetric Steglich and Black rearrangements have been developed.[4,5] However, limited examples are reported for intermolecular enantioselective *C*-acylation of enolates or enol ethers.[6,7,8] A challenging issue for *C*-acylation is competitive *O*-acylation, leading to mixtures of *C*- and *O*-acylated products.[9] Fu has reported an excellent strategy for *C*-acylation of silyl ketene acetals utilizing planar-chiral 4-(pyrrolidino)pyridine (PPY) catalysts, which allows access to cyclic and acyclic β-keto esters with excellent enantioselectivity.[6] Alternative strategies involve isothiourea or thiourea catalyzed *C*-acylation of silyl ketene acetals as reported by Smith and Jacobsen.[7,8] To the best of our knowledge, there have been no reports of intermolecular enantioselective *C*-acylation reactions of carbonyl derivatives other than silyl ketene acetals. Herein, we report a new strategy for catalytic enantioselective *C*-acylation that enables the preparation of lactams bearing α-quaternary stereocenters.

We have reported several strategies for the transition-metal-catalyzed enantioselective construction of quaternary stereocenters.[2] In the course of our investigations on enolate functionalizations, we discovered that an α-acylated product (**4a**) is produced by the reaction of the lithium enolate derived from lactam **1a** in the presence of benzonitrile (**2a**), chlorobenzene (**3a**), and a Ni(0) precatalyst (Table 1, entry 1).[10] Initially, we imagined that **4a** could be formed by direct nucleophilic addition of the lithium enolate of lactam **1a** to benzonitrile **2a** followed by hydrolysis of the resulting imine. Therefore, we conducted a series of control experiments to confirm the reaction pathway. Contrary to our expectations, in the absence of $Ni(COD)_2$ and BINAP the reaction did not produce the product **4a**, and only trace amount of product was obtained from the reaction in the absence of ligand (entries 2 and 3). Most interestingly, the reaction did not proceed without aryl chloride **3a** (entry 4). Notably, Pd(0) and Ni(II) did not promote the reaction (entries 5 and 6). Finally, as we observed product **4a** when substituting chlorotoluene for chlorobenzene in the reaction, we elucidated that the source of the α-benzoyl group present in the product is indeed benzonitrile (**2a**) and not the corresponding chloroarene.[11]

Table 1. Discovery of a Ni-catalyzed enolate acylation[a]



entry	deviation from standard conditions	yield (%)
1	none	31
2	no $Ni(COD)_2$ or (*R*)-BINAP	0
3	no (*R*)-BINAP	3[b]
4	no PhCl	0
5	$Pd(dba)_2$ instead of $Ni(COD)_2$	0
6	$NiCl_2$ instead of $Ni(COD)_2$	0
7	*p*-tolylCl instead of PhCl	41

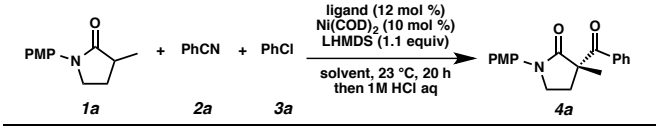
[a]Conditions: lactam (1 equiv), PhCN (2 equiv), aryl chloride (2 equiv), LHMDS (1.1 equiv), $Ni(COD)_2$ (10 mol %), ligand (12 mol %), in 5:1 toluene-THF (0.2 M) at 23 °C for 20 h, then 1 M HCl aq at 23 °C for 0.5 h. [b]HPLC conversion.

With a reasonable handle on the reaction pathway, we turned our attention toward optimization of the reaction conditions, with an emphasis on enantioselective catalysis. We examined the *C*-acylation of lactam **1a** using a variety of chiral ligands (12 mol %) with $Ni(COD)_2$ (10 mol %) and LHMDS (1.1 equiv) in a range of solvents at 23 °C (Table 2).[12] As a result of this study, Mandyphos-type ligands (e.g., **L2** and **L3**) emerged as promising can-

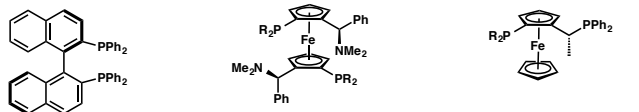
didates, displaying good enantioselectivity and reactivity. Further examination revealed that a Josiphos-type ligand (i.e., **L4**) in TBME promotes the reaction with greater enantioselectivity (–60% ee) and conversion (74%).

Further studies aimed toward optimization of bases, aryl halides, and additives are summarized in Table 3. No enantioselectivity was observed in reactions using NaHMDS or KHMDS instead of LHMDS (entries 2–4), which was attributed to the formation of aryne intermediates under these conditions.[13] Bromobenzene (**3b**) exhibited superior enantioselectivity and reactivity compared to chlorobenzene (**3a**, cf. entries 2 and 5), iodobenzene (**3c**, cf. entries 6 and 5), and phenyl triflate (**3d**, cf. entries 7 and 5). Encouraged by these results, we examined lithium salt additives. To our delight, reactivity and enantioselectivity were improved dramatically by adding LiBr, especially using the Mandyphos-type ligands (entries 9 and 10).[14,15]

Table 2. Ligand and solvent optimization



ligand	solvent (conversion / ee)					
	toluene	THF	dioxane	TBME	DME	toluene–THF (5:1)
L1	31% / –7% ee	–	–	–	–	–
L2	70% / 59% ee	32% / 15% ee	52% / 47% ee	72% / 51% ee	53% / 25% ee	53% / 52% ee
L3	71% / 62% ee	29% / 13% ee	42% / 47% ee	42% / 31% ee	47% / 21% ee	45% / 53% ee
L4	79% / –30% ee	26% / –2% ee	52% / –30% ee	74% / –60% ee	37% / –6% ee	54% / –41% ee



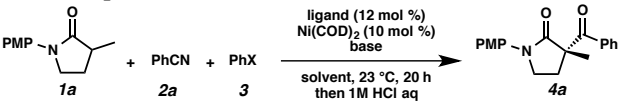
L1: (R)-BINAP

L2: SL-M004-1 (R = 4-MeO-3,5-Me2Ph)
L3: SL-M009-1 (R = 3,5-Me2Ph)

L4: SL-J006-1 (R = 3,5-(CF3)2Ph)

[a]Conditions: lactam (1 equiv), PhCN (2 equiv), PhCl (2 equiv), LHMDS (1.1 equiv), $Ni(COD)_2$ (10 mol %), ligand (12 mol %), in solvent (0.2 M) at 23 °C for 20 h, then 1 M HCl (aq) at 23 °C for 0.5 h.

Table 3. Optimization of the reaction conditions

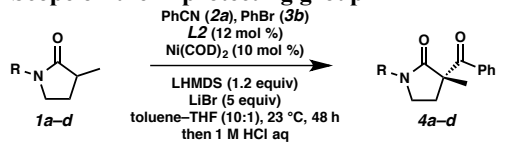


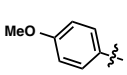
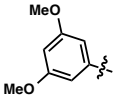
entry	ligand	base	PhX	solvent	additive	conversion (%)	ee (%)
1[a]	*L4*	tBuOLi	PhCl *3a*	TBME	–	0	0
2[a]	*L4*	LHMDS	PhCl *3a*	TBME	–	74	–54
3[a]	*L4*	NaHMDS	PhCl *3a*	TBME	–	42	0
4[a]	*L4*	KHMDS	PhCl *3a*	TBME	–	51	0
5[a]	*L4*	LHMDS	PhBr *3b*	TBME	–	83	–61
6[a]	*L4*	LHMDS	PhI *3c*	TBME	–	65	–55
7[a]	*L4*	LHMDS	PhOTf *3d*	TBME	–	73	–28
8[b]	*L2*	LHMDS	PhBr *3b*	toluene–THF (10:1)	–	55	68
9[b]	*L2*	LHMDS	PhBr *3b*	toluene–THF (10:1)	LiBr (5 equiv)	98	89
10[b]	*L3*	LHMDS	PhBr *3b*	toluene–THF (10:1)	LiBr (5 equiv)	92	89
11[b]	*L4*	LHMDS	PhBr *3b*	toluene–THF (10:1)	LiBr (5 equiv)	28	–46

[a]Conditions: lactam (1 equiv), PhCN (2 equiv), PhX (2 equiv), base (1.1 equiv), $Ni(COD)_2$ (10 mol %), ligand (12 mol %), in solvent (0.2 M) at 23 °C for 20 h, then 1 M HCl aq at 23 °C for 0.5 h. [b]Conditions: lactam (2 equiv), PhCN (1 equiv), PhX (1 equiv), base (1.2 equiv), $Ni(COD)_2$ (10 mol %), ligand (12 mol %), in solvent (0.2 M) at 23 °C for 20 h, then 1 M HCl aq. 0.5 h at 23 °C.

We then examined the effect of substituents on the *N*-aryl fragment of the lactam substrate. Several lactams (**1a–d**) were prepared and subjected to the optimized acylation conditions (Table 4). Lactam **1b** displayed slightly superior enantioselectivity to **1a**, although acylated product **4b** was produced in moderate yield at ambient temperature. Gratifyingly, reaction at 4 °C led to improved yield of lactam **4b**. Derivatives **1c** and **1d** had similar enantioselectivity as the parent PMP-lactam **1a**. In general, a fair amount of substitution around the *N*-aryl group is tolerated in the reaction process affording acylated lactams in good yields and with high ee. It should be noted that we observed optimal conversion and ee using a 2:1 lactam:PhCN ratio, which are the conditions we used for our substrate scope (see Supporting Information). However, in order to increase the synthetic practicality of the reaction we were able to lower the ratio to 1.2:1 lactam:nitrile to give comparable results (89% conversion, 87% ee). On a gram-scale with reduced equivalents of lactam (1.3 equiv), **1a** underwent acylation smoothly to furnish 1.1 g of **4a** in 69% yield and 90% ee. Finally, we attempted reactions with δ-valerolactams, but achieved low product formation with good ee (13% yield, 77% ee) under these conditions.

Table 4. Scope of the *N*-protecting group[a]

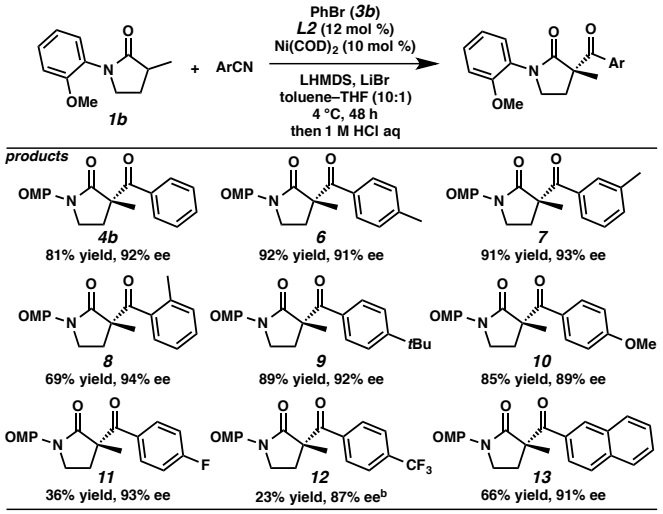


R				
	1a→4a	*1b→4b*	*1c→4c*	*1d→4d*
yield, ee	86%, 88% ee[b]	61%, 92% ee[b] 81%, 92% ee[c]	80%, 85% ee[c]	69%, 86% ee[c]

[a]Conditions: lactam (2 equiv), PhCN (1 equiv), PhBr (1.5 equiv), LHMDS (1.2 equiv), LiBr (5 equiv), $Ni(COD)_2$ (10 mol %), ligand (12 mol %), in toluene–THF (10:1, 0.09 M), then 1 M HCl aq. [b]Reactions were conducted at 23 °C for 24 h. [c]Reactions were conducted at 4 °C for 48 h.

With the optimized conditions in hand, we explored the substrate scope of this enantioselective *C*-acylation reaction (Tables 5 and 6). Generally, the process is tolerant of a wide range of substituents and functionality on both the aryl nitrile and the parent lactam substrate. Aryl nitriles having both electron-donating and electron-withdrawing substituents at the *para* position can be successfully applied, leading to products with excellent enantioselectivities (e.g., Table 5, **6**, **9–12**). Despite the uniformly high ee, electron-withdrawing substituents on the nitrile furnish products in significantly diminished yields (e.g., **11**, **12**).[16] The reaction is also not impacted to a large degree when the nitrile is substituted at either the *meta* or *ortho* position (e.g., **7**, **8**). Lastly, we unfortunately observed no reactivity when alkyl nitriles were assayed.

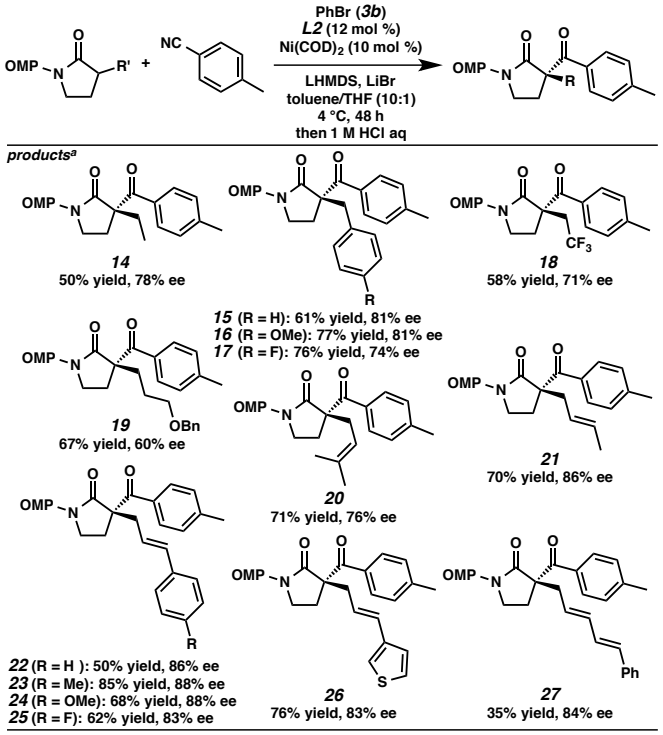
Table 5. Enantioselective *C*-acylation of lactams; Scope of the nitrile[a]



[a]Conditions: lactam (2 equiv), ArCN (0.2 mmol, 1 equiv), PhBr (1.5 equiv), base (1.2 equiv), $Ni(COD)_2$ (10 mol %), ligand (12 mol %), in toluene–THF (10:1, 0.09 M) at 4 °C for 48 h, then 1 M HCl aq. [b]The reaction was carried out at 23 °C for 24 h.

The scope of substitution at the lactam α-carbon is illustrated in Table 6. Although the enantioselectivity tends to decrease with larger α-substituents, examples having ethyl, benzyl, substituted-benzyl and substituted-allyl groups all furnished the *C*-acylated products with good enantioselectivities (74–88% ee). Crotyl- and cinnamyl-substituted lactams were particularly effective in the acylation, providing interesting lactam products in high ee (e.g., **21**–**25**).

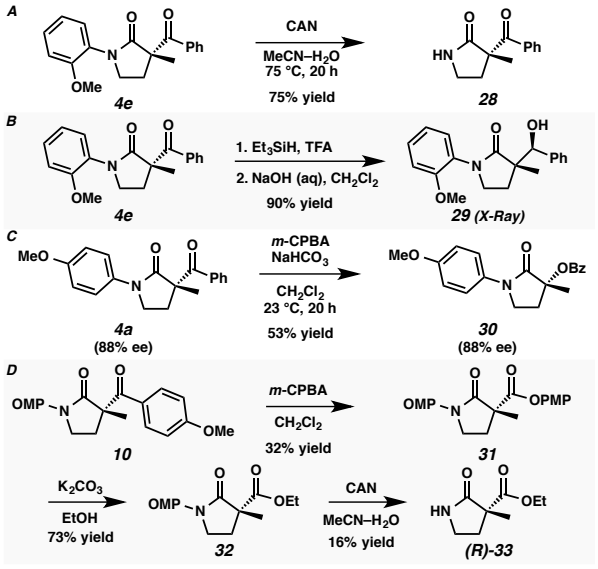
Table 6. Enantioselective *C*-acylation of lactams; scope of the lactam α-substiuent[a]



[a]Conditions: lactam (2 equiv), *p*-tolunitrile (0.2 mmol, 1 equiv), PhBr (1.5 equiv), base (1.2 equiv), $Ni(COD)_2$ (10 mol %), ligand (12 mol %), in toluene–THF (10:1, 0.09 M) at 4 °C for 48 h, then 1 M HCl aq.

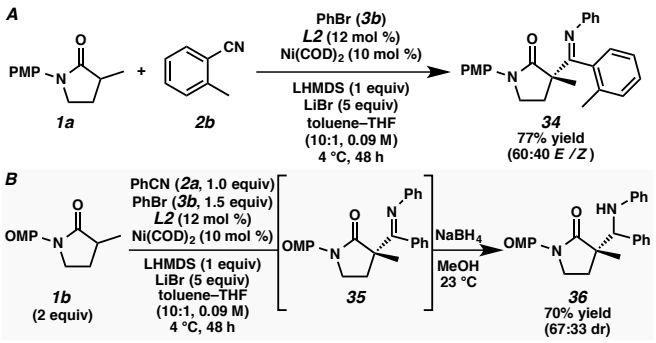
To demonstrate the synthetic utility of our enantioselective lactams acylation, we carried out transformations on the enantioenriched lactam products generated in this study (Scheme 1). The *o*-methoxy protecting group of lactam **4e** was easily removed by CAN oxidation to form lactam **28** (Scheme 1A).[17] Reduction of ketone **4e** with Et_3SiH proceeded with perfect diastereoselectively and afforded alcohol **29** as a single isomer in excellent yield (Scheme 1B). The relative stereochemistry of lactam **29** was determined by single crystal X-ray diffraction (see Supporting Information). Lactam **4a** could be converted to α-benzoyloxy lactam **30** by Baeyer–Villiger oxidation, without loss of enantiopurity (Scheme 1C). Alternatively, Baeyer–Villiger oxidation of lactam **10** gave α-aryloxycarbonyl lactam **31** (Scheme 1D). The PMP ketone directs the regioselectivity of the Baeyer–Villiger oxidation and allows for the asymmetric synthesis of α-carboxy lactam derivatives.[18] To determine the absolute stereochemistry, **31** was converted to known lactam derivative **33** by ester exchange followed by deprotection of the *o*-methoxyphenyl group. The specific optical rotation of carboxylactam **33** corresponded to the reported value for (*R*)-**33**.[19] The absolute configurations of all acylated lactam products in this manuscript are presented by analogy to this finding.

Scheme 1. Derivatization of *C*-acylated products and determination of absolute stereochemistry



To clarify the reaction pathway, we attempted to isolate the putative imine intermediate.[11] Fortuitously, by avoiding an acidic aqueous work-up and carefully chromatographing of the crude reaction mixture, we were indeed able to isolate imine **34**, which was obtained as a 60:40 *E/Z* mixture from the reaction of lactam **1a** with *o*-tolunitrile **2b** and bromobenzene **3b** (Scheme 2A). Additionally, we were able to prepare amine **36** as a 63:37 diastereomeric mixture by in situ reduction of imine intermediate **35** (Scheme 2B). These experiments provide further evidence that an *N*-arylated imine (e.g., **5a**, **34**, and **35**) is likely the direct product of the catalytic reaction.

Scheme 2. Isolation and reduction of imine intermediate



Taking these results into consideration, we illustrate a possible reaction mechanism for our *C*-acylation reaction in Figure 1. We envision that the reaction proceeds by a Ni^0/Ni^{II} redox catalytic cycle. Oxidative addition of the aryl bromide to a Ni^0 complex (i.e., **A**) produces a Ni^{II} arene species (**B**). Ligand substitution and insertion of the benzonitrile and lactam enolate is envisioned to be stereodetermining and to produce Ni^{II}-imino complex **C**. Reductive elimination from **C** leads to the primary imine product and regenerates Ni^0 complex **A**. The *C*-acylated product is ultimately furnished by hydrolysis of the imine in aqueous acid.

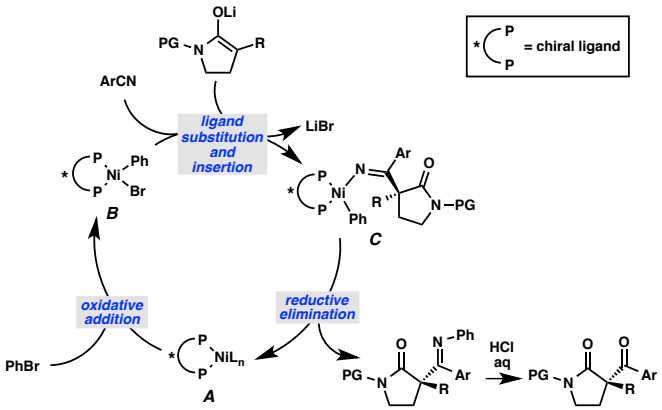


Figure 1. Plausible reaction mechanism of enantioselective *C*-acylation.

In summary, we have developed the first intermolecular enantioselective *C*-acylation of lactams by applying a chiral Ni catalyst. The process is nominally a three-component coupling reaction involving a lithium enolate, a benzonitrile, and an aryl halide. Critical to the success of this new reaction is the implementation of a readily available Mandyphos-type ligand and the addition of excess lithium bromide, the combination of which afforded high enantioselectivity and yield in the acylation. Future work will focus on expanding the scope of the reaction, elucidating the stereochemical course and mechanistic details of the process, and implementation of this new chemistry in the context of multistep synthesis.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, single crystal X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

The authors wish to thank NIH-NIGMS (R01GM080269), Daiichi-Sankyo Co., Ltd. (M. H.), JSPS (S. H.), MEXT (S. H.), the Caltech 3CS, and Caltech for financial support. C.C.E. also thanks Loyola University Chicago for financial support. Mr. Hashiru Negishi (Caltech), Mr. Larry Henling (Caltech), and Dr. Scott Virgil (Caltech) are acknowledged for helpful discussions, instrumentation, and experimental assistance.

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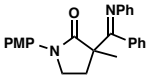
(11) We have observed *N*-phenyl imine intermediate **5a** by mass spectrometric analysis of the crude reaction mixture.



5a

(12) For a full listing of ligands evaluated, see Supporting Information.

(13) Under similar conditions, we have observed that NaHMDS and KHMDS in the presence of a substituted aryl halide result in two constitutional isomers of cross-coupled product, which we hypothesize arise from aryne intermediacy.

(14) For a more detailed study of additive effects, see Supporting Information.

(15) The beneficial effect of LiBr may be due to increasing the ionic strength of the reaction medium or altering the speciation of lithium enolate aggregates. For related references, see (a) Juaristi, E.; Beck, A. K.; Hansen, J.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis*, **1993**, *12*, 1271. (b) Fagnou, K.; Lautens, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 26. (c) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832. (d) Liang, Y.; Fu, G. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 9047. (e) Son, S. Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756.

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TOC Graphic