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Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α-Disubstituted Ketones

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Supporting Information

ABSTRACT: The first enantioselective Ni-catalyzed reductive acyl cross-coupling has been developed. Treatment of acid chlorides and racemic secondary benzyl chlorides with a Ni^{II}/bis(oxazoline) catalyst in the presence of Mn^0 as a stoichiometric reductant generates acyclic α,α-disubstituted ketones in good yields and high enantioselectivity without requiring stoichiometric chiral auxiliaries or pregeneration of organometallic reagents. The mild, base-free reaction conditions are tolerant of a variety of functional groups on both coupling partners.

Enantioenriched acyclic α,α-disubstituted carbonyl compounds are versatile synthetic intermediates for the synthesis of natural products and pharmaceutical agents. Due to their ubiquity and utility, the development of new synthetic methods to prepare such compounds has been the subject of intense research. In addition to numerous chiral auxiliary-based strategies,[1] there are an increasing number of catalytic asymmetric α-alkylation,[2] -alkenylation,[3] and -arylation[4] reactions that provide products with α-tertiary stereogenic centers. Collectively, these methods represent a versatile array of tools that are indispensible to synthetic chemists.

The vast majority of α-functionalization reactions described above proceed via the intermediacy of enolates or enolate equivalents. As a result, the stereochemistry of C−C bond formation is typically influenced by both the enolate geometry and the π-facial selectivity. The synthesis of acyclic α,α-disubstituted *ketones* presents the added requirements of (1) site-selective enolization and (2) mild conditions that prevent racemization of the newly formed tertiary stereogenic center.[5,6] Strategically, we envisioned that transition-metal-catalyzed acyl cross-coupling reactions, which typically occur at low temperatures and circumvent enolate intermediates altogether, could represent an alternative approach to prepare enantioenriched acyclic α,α-disubstituted ketones in a convergent and regioselective fashion.[7] Specifically, we hypothesized that Ni-catalyzed *reductive* coupling reactions[8,9] between carboxylic acid derivatives and secondary alkyl halides[10] could be amenable to asymmetric catalysis (Figure 1).[11,12] Although several different mechanisms have been proposed for these reactions, one possibility is that the catalytic cycle involves oxidative addition of the alkyl halide to a Ni^I-acyl complex.[11d] If this oxidative addition step were to occur by a radical mechanism, as is proposed for other Ni-catalyzed stereoconvergent reactions of alkyl halides,[13] use of a chiral nickel catalyst could enable the stereoconvergent synthesis of enantioenriched α,α-disubstituted ketones from racemic alkyl halides. Herein we report the successful execution of this plan, which has resulted in the development of the first enantioselective Ni-catalyzed reductive cross-coupling reaction between acid chlorides and secondary alkyl halides.

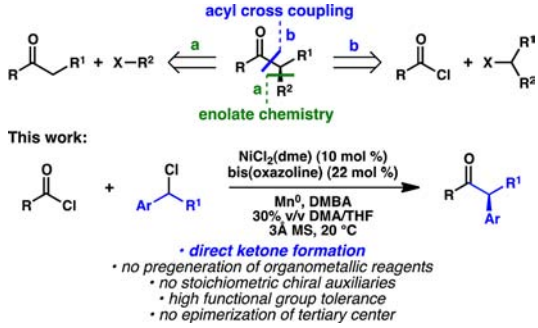
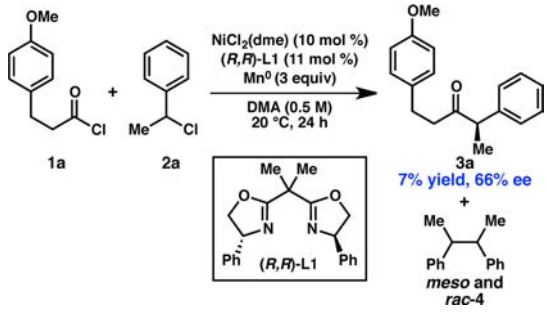


Figure 1. Design considerations.

Our investigations began with the reductive coupling of 3-(4-methoxyphenyl)propionyl chloride (**1a**) and (1-chloroethyl)-benzene (**2a**). Using catalytic $NiCl_2$(dme) in dimethylacetamide (DMA) with Mn^0 as the stoichiometric reductant, conditions previously reported to promote the coupling of acid chlorides and alkyl halides,[11c] a screen of chiral ligands was conducted. We were pleased to find that use of commercially available (*R*,*R*)-diphenyl-BOX ((*R*,*R*)-**L1**) provided the desired ketone product **3a** with 66% ee, albeit in a very low yield. The major byproducts were a mixture of *rac*- and *meso*-dibenzyl **4** (Scheme 1), which

Scheme 1. Lead Conditions for the Enantioselective Formation of 3a



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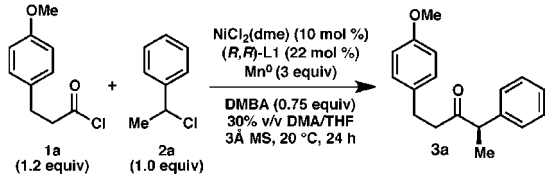
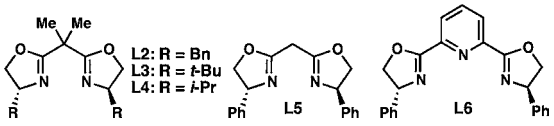
result from homocoupling of **2a**.[14] Following an extensive study of reaction parameters, it was determined that the addition of **1a** and **2a** to a mixture of catalytic $NiCl_2$(dme), (*R*,*R*)-**L1**, 2,6-dimethylbenzoic acid (DMBA, **5**), and 3 Å molecular sieves with Mn^0 (3 equiv) as the stoichiometric reductant provided ketone **3a** in 85% yield and 92% ee (Table 1, entry 1).

Table 1. Impact of Reaction Parameters on Ni-Catalyzed Asymmetric Reductive Coupling



entry	deviation from standard conditions[a]	conv. **2a** (%)[b]	yield **4** (%)[b]	yield **3a** (%)[b]	ee **3a** (%)[c]
1	**none**	**90**	**4**	**85**	**92**
2	no Mn^0	0	0	0	–
3	no $NiCl_2$(dme)	35	35	0	–
4	no **L1**	73	5	8	–
5	no DMBA (5)	100	22	52	94
6	no 3 Å MS	100	7	76	90
7	Zn^0 instead of Mn^0	85	26	31	88
8	$Ni(COD)_2$ instead of $NiCl_2$(dme)	98	18	68	92
9	$CoCl_2$ instead of $NiCl_2$(dme)	73	24	0	–
10	**L2** instead of **L1**	61	24	22	45
11	**L3** instead of **L1**	98	62	14	2
12	**L4** instead of **L1**	89	52	40	69
13	**L5** instead of **L1**	15	1	10	0
14	**L6** instead of **L1**	99	53	4	9
15	11 mol % **L1**	82	3	72	92
16	DMA as solvent	99	43	30	88
17	THF as solvent	25	<1	26	94
18	MeCN as solvent	28	4	16	45
19	AcOH instead of **5**	96	17	65	92
20	PivOH instead of **5**	97	51	33	92
21	BzOH instead of **5**	73	14	40	92
22	(1-bromoethyl)benzene instead of **2a**	100	42	58	92

[a]Reactions conducted on 0.2 mmol scale under a N_2 atmosphere in a glovebox. [b]Determined by GC versus an internal standard. [c]Determined by SFC using a chiral stationary phase.

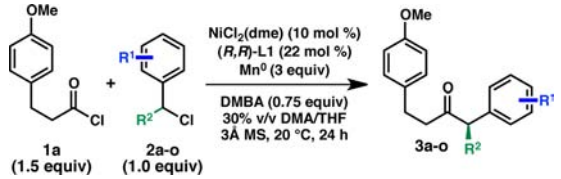


Control experiments determined that ketone **3a** is not produced in the absence of the Mn^0 or Ni catalyst, although low yields of **3a** can be observed in the absence of ligand (Table 1, entries 2–4). During our preliminary studies, the yields of **3a** were found to be inconsistent, which led to the hypothesis that variable amounts of 3-(4-methoxyphenyl)propionic acid, resulting from hydrolysis of **1a**, might influence the efficiency of the reaction. Indeed, the addition of exogenous carboxylic acids was found to decrease the formation of homocoupled product **4** and increase the yield of **3a** (entries 19–21), with DMBA providing the best results (entry 5).[15] Molecular sieves were discovered to further increase the yield of **3a** (entry 6). Given that Mn^0 mediates homocoupling of benzyl chloride **2a** in the absence of Ni (entry 3), several alternative stoichiometric inorganic and organic reductants were investigated with the objective of shutting down this undesired pathway. Unfortunately, Zn^0 was the only reductant that furnished detectable quantities of **3a**, and it did not provide improvements with respect to Mn^0 (entry 7). Use of $Ni(COD)_2$ as a precatalyst delivered **3a** with comparable ee (entry 8). However, the yield was reduced relative to $NiCl_2$(dme); use of other metal salts such as $CoCl_2$ were ineffective (entry 9).

A reinvestigation of ligands under the optimized conditions confirmed that **L1** provides higher ee's than other substituted bis(oxazolines) (entries 10–14). Furthermore, the isopropylidene bridge of **L1** proved to be critical, as **L5** afforded **3a** with no stereoinduction. Tridentate ligands such as **L6** led to almost exclusive homocoupling.[16] The mixed solvent system was found to provide the appropriate balance of reactivity and selectivity (entries 16–18). Whereas the best ee's were obtained in THF, the reactivity was poor and the yields were low. DMA provided higher conversions, however increased production of homodimer **4** was also observed. Reducing the **L1**:Ni ratio to 1.1:1 led to a slight reduction in yield of **3a** (entry 15). Coupling of (1-bromoethyl)benzene under otherwise identical reaction conditions provided **3a** in the same ee, but in lower yield due to increased formation of **4** (entry 22).[17,18]

With optimized conditions in hand, we investigated the scope of the benzyl chloride (Table 2). Coupling of **1a** with benzyl chlorides bearing electron-releasing substituents furnished the corresponding ketones in high ee; however, these substrates reacted slowly relative to **2a** and required higher **L1**:Ni ratios (3.3:1) to obtain good conversions (entries 2–5). In contrast, benzyl chlorides bearing electron-withdrawing substituents reacted rapidly and proceeded to full conversion. In the case of

Table 2. Substrate Scope of Benzyl Chlorides



entry	R^1	R^2	Pdt	yield (%)[a]	ee (%)[b]
1	H	Me	**3a**	79	93
2[c]	4-Me	Me	**3b**	74	93
3[c]	3-Me	Me	**3c**	75	93
4[c]	2-Me	Me	**3d**	35	72
5[c]	4-OMe	Me	**3e**	56	86
6	4-Cl	Me	**3f**	76	91
7[d]	4-Br	Me	**3g**	73	86
8[e]	4-CF_3	Me	**3h**	64	82
9[c]	2-naphthyl	Me	**3i**	65	91
10	H	Et	**3j**	50	94
11	Cl	Et	**3k**	65	90
12	H	Bn	**3l**	79	92
13[f]	H	CH_2OTBS	**3m**	51	89
14	H	4-pentenyl	**3n**	38	92
15	2,3-dihydro-1*H*-inden-1-yl		**3o**	68	78

[a]Isolated yield; reactions conducted on 0.2 mmol scale under a N_2 atmosphere in a glovebox. [b]Determined by SFC using a chiral stationary phase. [c]Run with 33 mol % (*R*,*R*)-**L1**. [d]Run with 1.25 equiv of DMBA [e]Run in 20% v/v DMA/THF. [f]Run in 50% v/v DMA/THF.

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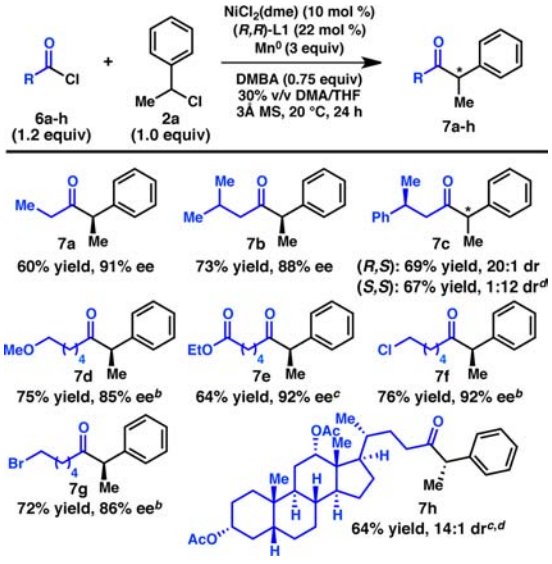
the trifluoromethyl-substituted substrate (entry 8), the higher reactivity was accompanied by increased side product formation and somewhat reduced enantioselectivity. Both 4-chloro- and 4-bromobenzyl chlorides can be coupled with complete chemoselectivity, providing products suitable for further elaboration. Under our standard conditions, the coupling of **2g** resulted in higher-than-usual levels of homocoupling: this was mitigated via addition of excess DMBA (entry 7). Unfortunately, *o*-substituted benzyl chlorides (e.g., **2d**, entry 4) were poor substrates, providing the ketone products in low yields and ee's.

We were pleased to discover that β-substituted benzyl chlorides provide access to α-aryl-α-alkyl ketones with high enantioselectivity (entries 10−14). In general, these substrates react more slowly and do not achieve complete conversion; however, they also exhibit a low propensity toward homocoupling. Interestingly, **3n** was formed without any detectable quantities of the 5-*exo* cyclization product (entry 14). This result suggests that if oxidative addition takes place via a radical pathway, then radical recombination occurs faster than cyclization or that the radical cyclization is reversible.[19] In addition, the reaction can be run on preparative scale: coupling of acid chloride **1a** and benzyl chloride **2a** on a 1.0 mmol scale at the benchtop delivered ketone **3a** in 70% yield and 93% ee.

The scope of the acid chloride coupling partner was also investigated (Table 3). Alkyl halide and ester functionalities are

Table 3. Substrate Scope of Acid Chlorides[a]



[a]Isolated yield; reactions conducted on 0.2 mmol scale under a N_2 atmosphere in a glovebox. % ee determined by SFC using a chiral stationary phase. [b]Run in 20% v/v DMA/THF. [c]Run in 10% v/v DMA/THF. [d]Run with (*S*,*S*)-**L1**.

well tolerated; these findings are noteworthy because such groups would not be compatible in their native form with the more conventional synthesis involving auxiliary-controlled alkylation followed by Weinreb ketone synthesis.[20] For several of the acid chlorides shown in Table 3, the efficiency of the coupling proved to be sensitive to the DMA/THF ratio, with improved yields often being observed with lower levels of the amide solvent. Depending on the enantiomer of **L1** that is employed, the coupling of **2a** with enantiopure acid chloride **6c** provides access to either diastereomer with high diastereoselectivity. A standard enolate alkylation approach to **7c** would not be anticipated to provide such high levels of 1,4-stereoinduction. The power of this methodology is further demonstrated by the diastereoselective preparation of ketone **7h**.

Although further investigations are required, one possible mechanism is the sequential reduction catalytic cycle proposed in Figure 2.[21,22] Oxidative addition of the acid chloride could

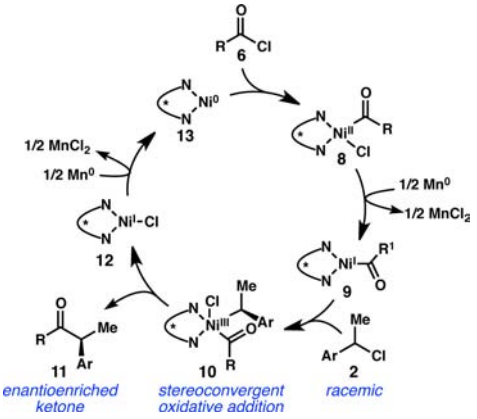


Figure 2. Possible catalytic cycle.

generate Ni^{II}-acyl complex **8**, which could be reduced by Mn^0 to give Ni^{I}-acyl species **9**. Subsequent oxidative addition of benzyl chloride **2** by a radical process would then generate Ni^{III} complex **10**, converging both enantiomers of **2** to a single diastereomer. This step of the mechanism resembles that proposed for Ni-catalyzed stereoconvergent cross-coupling reactions between secondary alkyl halides and organometallic reagents.[13a,23] Reductive elimination of ketone **11** from **10** followed by reduction of the Ni^{I}-chloride complex would close the catalytic cycle.[24]

In conclusion, the first Ni-catalyzed asymmetric reductive acyl cross-coupling reaction has been developed. This mild, chemoselective reaction provides access to a variety of α-aryl-α-alkyl ketones in good yields and high enantioselectivity. The reaction is highly convergent and functional group tolerant, which enables the rapid construction of complex ketones from bench stable, easy-to-handle starting materials. The further development and application of this reaction, as well as study of the mechanism, is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, compound characterization data, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) A control experiment employing the mixed anhydride derived from **1a** and DMBA delivered **3a** in 44% yield and 92% ee. However, mixing of **1a** and DMBA in 30% v/v DMA/THF with 3 Å MS does not result in formation of the mixed anhydride **1b**. Due to challenges associated with in situ monitoring of this heterogeneous reaction, we cannot definitively establish whether **1b** is formed in situ and is the reactive substrate, or whether both **1b** and **1a** converge to a common intermediate in the catalytic cycle.

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(17) The ee of ketone **3a** is constant over the course of reaction, whereas the ee of recovered **2a** gradually increases to 17% at 94% conversion. These results suggest that the two enantiomers of **2a** react at comparable rates, as only a very modest kinetic resolution occurs. When enantioenriched **2a** is employed, ketone **3a** is obtained in 92% ee and **2a** is recovered without erosion of ee.

(18) The absolute stereochemistry of ketone **7a** was assigned by comparison of the optical rotation to literature reported data. (a) Rodríguez, C.; de Gonzalo, G.; Fraaije, M. W.; Gotor, V. *Tetrahedron: Asymmetry* **2007**, *18*, 1338. See also ref 5e. The assignment of all other compounds was made by analogy.

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(22) For contrasting mechanistic proposals, see refs 11c, 11d and 12e.

(23) When the reaction between **1a** and **2a** is conducted in the presence of 0.5 equiv of the radical inhibitor 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT), ketone **3a** is produced in 80% yield and 92% ee. Alternatively, use of the electron transfer inhibitor 1-chloro-2,4-dinitrobenzene completely shuts down the reaction. These findings are consistent with the sequential reduction mechanism proposed in Figure 2.

(24) To assess the possibility of organomangenese intermediates, **1a** was converted to the corresponding benzylmanganese halide via Grignard formation/transmetalation and subjected to our optimized reaction conditions. Ketone **3a** was not produced under these conditions. For the formation of organomanganese reagents, see: (a) Boucley, C.; Cahiez, G.; Carini, S.; Cerè, V.; Comes-Franchini, M.; Knochel, P.; Pollicino, S.; Ricci, A. *J. Organomet. Chem.* **2001**, *624*, 223. (b) Cahiez, G.; Duplais, C.; Buendia, J. *Chem. Rev.* **2009**, *109*, 1434. (c) Peng, Z.; Knochel, P. *Org. Lett.* **2011**, *13*, 3198.