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# Synthesis of Acyclic Aliphatic Amides with Contiguous Stereogenic Centers via Pd-Catalyzed Enantio-, Chemo- and Diastereoselective Methylene C(sp$^3$)–H arylation

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Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry, CAS

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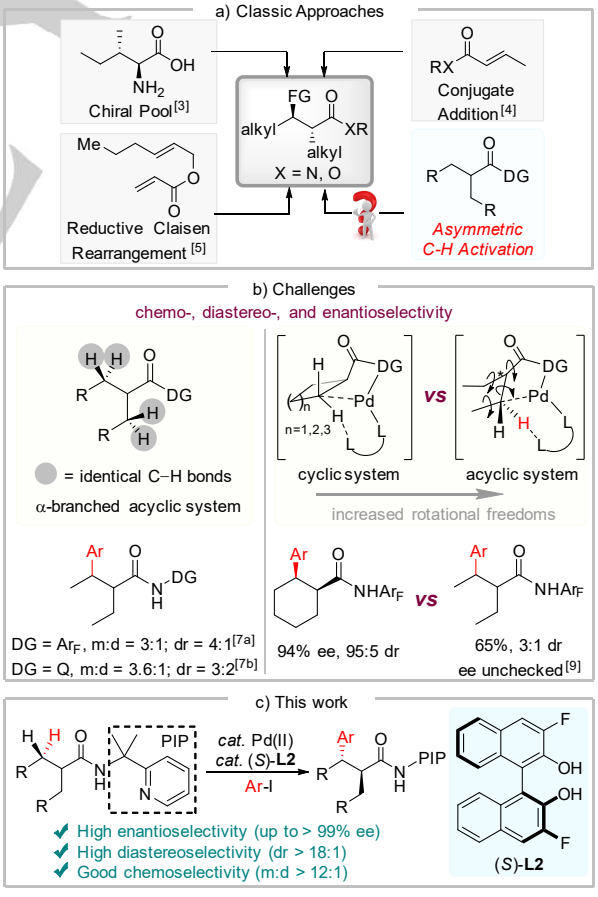
**Abstract:** The enantioselective desymmetrizing C–H activation of α-*gem*-dialkyl acyclic amides remains challenging because the availability of four chemically identical unbiased methylene C(sp$^3$)–H bonds and increased rotational freedoms of the acyclic systems add tremendous difficulties for chemo- and stereocontrol. Herein, we develop the synthesis of acyclic aliphatic amides with *α,β*-contiguous stereogenic centers via Pd(II)-catalyzed asymmetric arylation of unbiased methylene C(sp$^3$)–H in good yields and with high levels of enantio-, chemo- and diastereoselectivity (up to >99% ee and >20:1 dr). Successive application of this protocol enables the sequential arylation of the *gem*-dialkyl groups with two different aryl iodides, giving a range of β-Ar$^1$-β'-Ar$^2$-aliphatic acyclic amides containing three contiguous stereogenic centers with excellent diastereoselectivity.

Aliphatic acyclic amides containing *α,β*-contiguous stereogenic centers are a structural element widely found in natural products and biologically important compounds. For example, valnoctamide (2-ethyl-3-methyl valeramide, VCD, Nirvanil®) and its analogues featuring this framework have a board spectrum antiepieptic activity which are used for the treatment of neuropathic pain.[1] Although catalytic stereodivergent process has been well developed for the enantio- and diastereoselective creation of multiple stereocenters in a single-pot operation,[2] the construction of those chiral *α,β*-contiguous frameworks remains challenging. Current strategies rely on the multiple transformations from chiral pool precursors (e.g. amino acids),[3] asymmetric conjugate addition,[4] and reductive Claisen rearrangement[5] (Scheme 1a). To supplement these conventional methods, we sought to develop an enantio-, diastereo- and chemoselective methylene C(sp$^3$)-H functionalization of aliphatic carboxylic amides, a type of prevalent feedstocks in nature, as shown in Scheme 1a. The success of this strategy could provide a straightforward approach to these chiral architectures in a more atom- and step-economical manner. However, we were aware of the dearth of methods for enantioselective desymmetrizing C-H activation of α-*gem*-dialkyl acyclic amides.[6] Several challenges were noted as outlined in Scheme 1b. First, four chemically identical and equally accessible unbiased methylene C(sp$^3$)-H bonds within reach of the directing group (DG) raised significant




**Scheme 1.** Synthesis of α-branched acyclic amides containing *α,β*-contiguous stereogenic centers via enantioselective desymmetrizing C–H activation.

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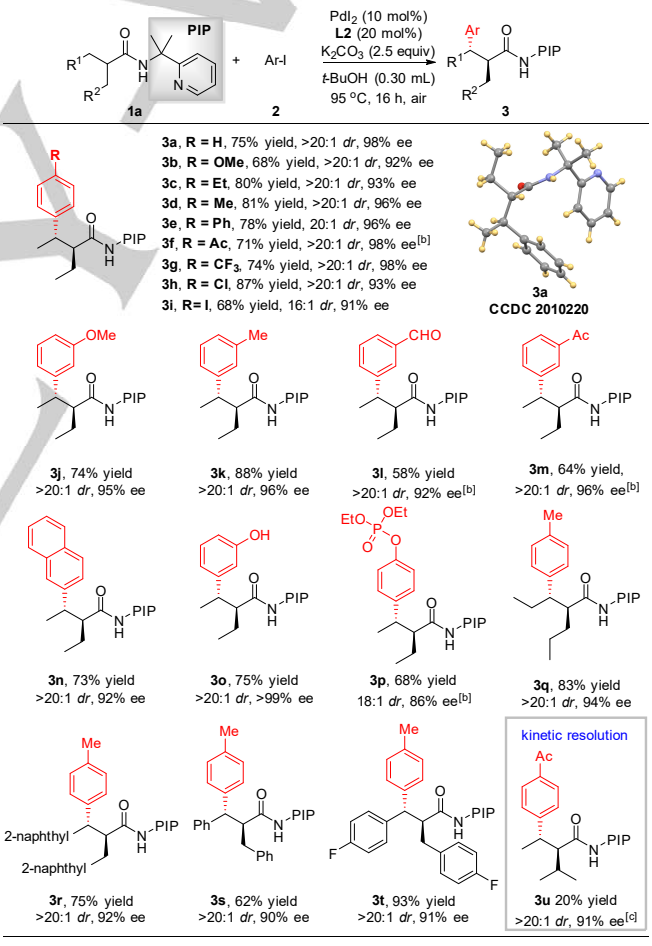
difficulties in controlling chemo- and stereocontrol. As a matter of fact, previous studies of the arylation of α-*gem*-diethyl acyclic amide led to poor mono-selectivity and diastereoselectivity (Scheme 1b, e.g. 2-ethyl-butyramide).[7] Second, desymmetrization of α-*gem*-dialkyl acyclic amides via asymmetric methylene C–H activation is fundamentally more challenging than the cyclic version and α-unbranched ones. The acyclic system has increased rotational freedoms, leading to the difficulty of stereocontrol. Therefore, although the enantioselective C–H functionalization of cycloalkane-type substrates have been well studied,[8-10] the adoption to the α-branched acyclic system generally gave unsatisfactory results.[9] For example, the Gooßen and Yu group achieved the Pd-catalyzed β-C-H arylation of methylene groups in cycloalkanes with high enantio- and diastereoinduction. However, when the procedure was applied to α-*gem*-dialkyl acyclic systems, the enantioselectivity and diastereoselectivity eroded drastically (Scheme 1b, cyclohexyl, 94% ee, 95:5 dr; α-diethyl, 3:1 dr, ee unchecked).[9,10] The flexibility of acyclic systems necessitates the judicious choice of proper chiral ligand and DG to enable the efficient stereoinduction and tune the reactivity. Herein, we describe our solution to this challenge by the combination of bidentate 2-pyridinyisopropyl (PIP) auxiliary and 3,3'-$F_2$-BINOL. This protocol enables the successful synthesis of acyclic aliphatic amides with *α,β*-contiguous stereogenic centers by desymmetric C-H arylation of *gem*-dialkyl C($sp^3$)–H bonds in high enantio-, diastereo- and chemoselectivity (Scheme 1c).

We initiated the investigations with the reaction of PIP-derived 2-ethylbutanoic amide (**1a**)[11,12] and iodobenzene (**2a**) in the presence of (*S*)-CPA,[13] a type of chiral ligand applied in desymmetrization of methylene C-H bonds,[13f] but very low chemo- and enantioselectivity was detected (m:d = 1.7:1, 2% ee, Table S1**,** entry 1). *t*-Bu-*N*-Boc-Leu, a privileged ligand widely used in asymmetric C-H activation,[14] was then tested. Even worse result was obtained (m:d = 0.9:1, 2% ee, entry 2). To our delight, when 3,3'-$F_2$-BINOL (*S*)-**L2** was used as ligand, high ee was obtained, albeit with moderate ratio of mono:di selectivity (Figure S1a, 90% ee, m:d = 3.8:1).[15,16] Various other 3,3'-disubstituted BINOLs (**L3-L9**) were also investigated and (*S*)-**L2** was found to be the optimal one (Figure S1a). Finally, high levels of enantio- and chemoselectivity was achieved by reducing the reaction temperature to 95 °C (**3a**, 75%, m:d = 12.5:1, 98% ee). We then evaluated the ligand effect on controlling chemoselectivity under the optimized reaction conditions (Figure S1b). Compared to the racemic reaction using $(BnO)_2PO_2H$ **L11** as ligand, the use of (*S*)-**L2** could significantly enhance the catalytic activity and improve the chemoselectivity [(*S*)-**L2: 3a**, 75%; **3aa**, 6% vs **L11: 3a**, 39%; **3aa**, 24%]. Further kinetic studies indicated (*S*)-**L2** could also significantly accelerate the reaction rate. The reaction of *rac*-**3f** with aryl iodide **2f** using (*S*)-**L2** as ligand led to the recovery of (2*S*, 3*S*)-**3f** in 58% yield with 48% ee. Therefore, we rationalized that the origin of good chemoselectivity might be partly due to the major enantiomer of the monoarylated product is difficult to undergo the diarylation while the minor enantiomer transforms into the diarylated product more easily, which also partly account for better enantioselectivity (Figure S1c).

With the optimized reaction conditions in hand, we then examined the scope of various aryl iodides (Table 1). In general, a range of electron-withdrawing and electron-donating substituents were tolerated well with high levels of diastereo- and enantioselectivity (>20:1 *dr*, 91% to 96% ee, **3a-3o**). Notably, iodide substituted on the *para*-position of the aryl iodide was also tolerated (68%, 16:1 *dr*, 91% ee, **3i**). It was worth mentioning that aryl iodides bearing free hydroxyl (75%, >20:1 dr, >99% ee, **3o**) and phosphonic acid diesters groups (68%, 18:1 *dr*, 86% ee, **3p**) were also survived, affording the products in good stereocontrol**.** Next, a series of aliphatic amides with other branched chains were examined. *gem*-Dipropyl aliphatic amides gave the corresponding products in good yield and stereoselectivity (83%, >20:1 *dr*, 94% ee, **3q**). Amides with sterically hinder groups at *β*-position (2-naphthyl, phenyl) were also compatible, giving good results (**3r-3t**, 62%-87% yield, >20:1 dr, 90%-92% ee). This protocol also showed synthetic potential for kinetic resolution, giving arylation product **3u** in high diastereo- and enantioselectivity (>20:1 *dr*, 90% ee), albeit with low conversion (20% yield). It's worth mentioning that all the reaction gave the corresponding mono-arylation products and only trace of di-arylation products could be observed on $^1$H NMR analysis of the crude products. The absolute configuration of arylation product **3a** was determined by X-ray crystallographic analysis.[17]

**Table 1.** Scope with respect to aryl iodides and aliphatic amides[a]




[a] Conditions A: **1a** (0.10 mmol), **2** (3.5 equiv), $PdI_2$ (10 mol%), $K_2CO_3$ (2.5 equiv), (*S*)-**L2** (20 mol%), *t*-BuOH (0.3 mL), 16 h, 95 °C under air. The *dr* value was determined by $^1$H NMR. Ee was determined by chiral HPLC. [b] Conditions B: **2** (2.0 equiv), *t*-BuOH (1.0 mL), 110 °C. [c] (*S*)-**L9** as ligand, **2f** (2.0 equiv).

The efficiency and practicality of this protocol was further proved by the compatibility with aryl iodides derived from complex organic molecules, such as natural products and drug molecules. The drug molecule, vinpocetine, was successfully incorporated at the proper position (**4a**, 64% yield, >20:1 *dr*, 96% ee). A series of

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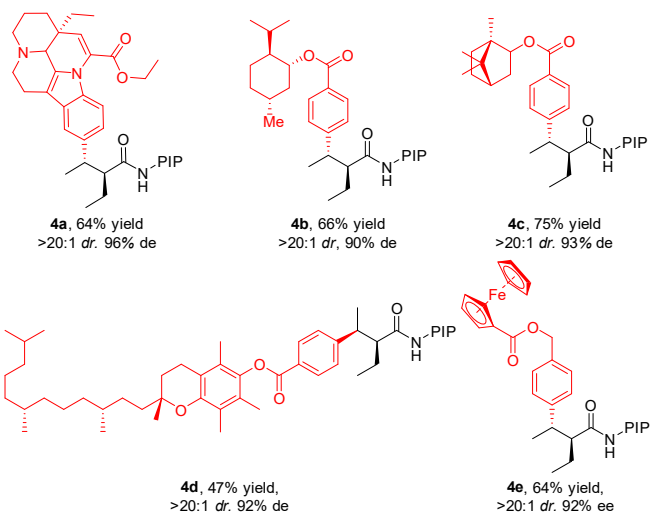
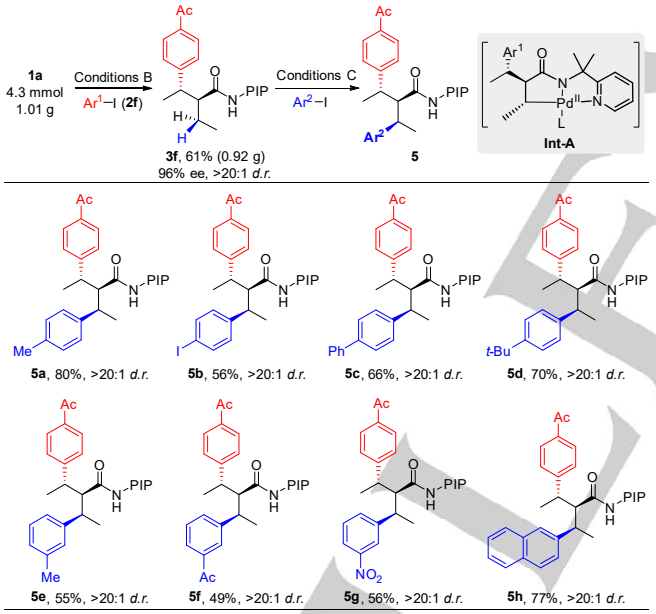
aryl iodides derived from natural products could also be effectively utilized and gave satisfactory results (**4a-4d**, >20:1 *dr*, 90% to 93% ee). A ferrocene moiety could also be introduced and well tolerated (**4e**, 64%, >20:1 *dr*, 92% ee).




**Scheme 2** Aryl iodides containing complex organic molecules.

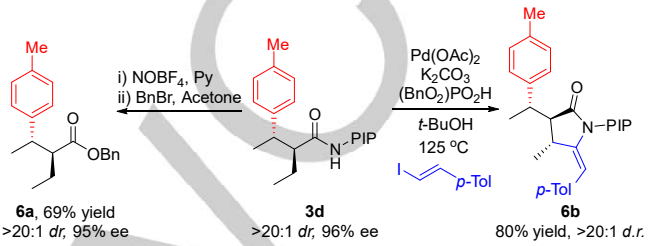
**Table 2** Subsequent arylation of the remaining unbiased methylene group[a]




[a] Conditions C: **3f** (0.10 mmol), **2** (2.0 equiv), $Pd(OAc)_2$. (10 mol%), $K_2CO_3$ (2.5 equiv), $(BnO)_2PO_2H$ (20 mol%), *t*-BuOH (1.0 mL), 16 h, 125 °C under air. The *dr* value was determined by $^1H$ NMR.

In our initial investigation, we observed that diarylation product **3aa** was obtained in 24% yield in the presence of $(BnO)_2PO_2H$ for the racemic condition (Figure S1b). We envisioned that the sequential arylation could enable the successful introduction of two distinct aryl groups, providing an efficient approach to prepare chiral aliphatic amides bearing three contiguous stereogenic centers. Thus, a gram-scale synthesis of monoarylated product **3f** was conducted first, affording 0.92 g **3f** with high stereocontrol (Table 2, 61%, 96% ee, >20:1 *dr*). After the asymmetric mono-arylation, subsequent diastereoselective *β*-methylene arylation with various different aryl iodides were performed, affording a myriad of aliphatic amides with three contiguous stereogenic centers (Table 2, **5a-5h**, 49%-80% yield, > 20:1 dr). The stereochemistry of **5a-5h** was assigned based on the formation of a sterically more favored *trans*-palladacycle **Int-A**.[18]

Finally, the PIP directing group could be easily removed by treating with $NOBF_4$[19] and followed by the formation of benzyl ester without erosion of enantiopurity (Scheme 3b, **6a**, 69%, 95% ee, >20:1 dr). Another unbiased *β*-methylene could be transformed through a highly diastereoselective Pd-catalyzed C-H alkenylation followed by an *aza*-Wacker cyclization sequence to form chiral γ-lactams **6b**, which could be further elaborated.[15c]




**Scheme 3** Synthetic transformations.

In summary, we reported the synthesis of acyclic aliphatic amides with contiguous stereogenic centers via Pd(II)-catalyzed asymmetric methylene C($sp^3$)–H arylation in good yields and with high level of enantio-, chemo- and diastereoselectivity for the first time. The readily available 3,3'-$F_2$-BINOL ligand plays a crucial role in distinguishing four chemically identical β-methylene C($sp^3$)-H and enhancing mono-selectivity. The protocol is scalable and applicable to a wide range of aryl iodides. The rapid preparation of chiral aliphatic amides bearing two or three contiguous centers provide a versatile platform for constructing α,β-chiral centers in asymmetric synthesis.

## Acknowledgements

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**Keywords:** palladium • C–H activation • enantioselectivity • diastereoselectivity • chemoselectivity • contiguous stereogenic centers

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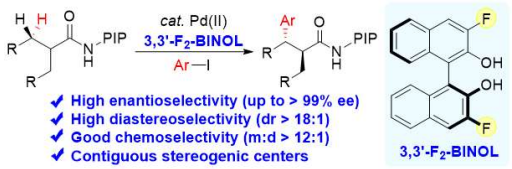


The enantioselective synthesis of acyclic aliphatic amides with contiguous stereogenic centers via Pd(II)-catalyzed asymmetric methylene C($sp^3$)–H arylation in good yields and with high levels of enantio-, chemo- and diastereoselectivity. The readily available 3,3'-$F_2$-BINOL ligand plays a crucial role in distinguishing four chemically identical β-methylene C($sp^3$)-H and enhancing mono-selectivity.

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