C–H Activation

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Pd^{II}-Catalyzed Enantioselective Activation of $C(sp^2)$–H and $C(sp^3)$–H Bonds Using Monoprotected Amino Acids as Chiral Ligands**

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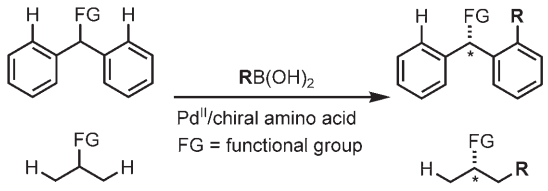
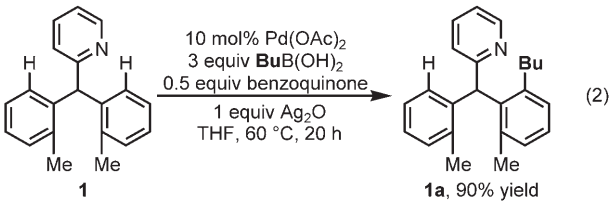
Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

Enantioselective C–H activation has been a longstanding challenge in catalysis and organic chemistry. The insertion of metal-bound carbenes or nitrenes into C–H bonds has been employed to develop highly enantioselective carbon–carbon and carbon–nitrogen bond-forming reactions.[1] The enantioselective lithiation of $C(sp^3)$–H bonds adjacent to the nitrogen atom in *N-tert*-butyloxycarbonylpyrrolidine using *sec*-BuLi/(−)sparteine has provided a broadly useful method for the differentiation of prochiral $C(sp^3)$–H bonds.[2] Investigations into the biomimetic oxidation of C–H bonds using chiral metal–porphyrin complexes[3] and other synthetic catalysts[4] continue to provide inspiration for the development of methods for the asymmetric oxidation of C–H bonds.

Remarkable progress in understanding the fundamental mechanisms of C–H activation by means of metal insertion[5] has spurred the development of metal-catalyzed carbon–carbon and carbon–heteroatom bond-forming reactions in organic molecules containing functional groups.[6] Such reactions will impact synthetic and medicinal chemistry in the context of retrosynthetic analysis[7] by providing unprecedented and more efficient strategic disconnections.[8] A major hurdle remaining in Pd^{II}-catalyzed C–H activation reactions, however, is the need for an external ligand that coordinates to the Pd^{II} species and controls the chemo-, regio-, and stereoselectivity of its insertion into C–H bonds. With this in mind, we embarked on the development of a Pd^{II}-catalyzed enantioselective C–H activation/C–C coupling reaction, a process previously unknown owing to the difficulty in differentiating prochiral C–H bonds through metal insertions.[9–11] Herein we demonstrate a proof of concept by the design of a Pd^{II}/amino acid complex capable of catalyzing asymmetric activation of prochiral $C(sp^2)$–H and $C(sp^3)$–H bonds to form chiral products with new C–C bonds in excellent enantioselectivity [Eq. (1)].



Directed C–H activation reactions assisted by functional groups within the substrate [Eq. (1)] were selected in this investigation. Success in asymmetric catalysis using this approach to control stereoselectivity has previously demonstrated its advantage and broad utility.[12] We began by developing an efficient C–H activation/C–C coupling reaction using the prochiral substrate **1**.[13] We hoped to use this reaction as a model system for enantioselective C–H activation directed by a wide range of functional groups. After screening various conditions, we found that the coupling of **1** with $BuB(OH)_2$ proceeded via a proposed six-membered palladacycle to give the desired racemic butylation product **1a** [Eq. (2)]. Benzoquinone (BQ) is required for the C–H



activation[14] and reductive-elimination steps.[15] Ag_2O reoxidizes the Pd^0 species back to Pd^{II} to close the catalytic cycle. The obtained triarylmethane derivatives are widely used in medicinal and material sciences.[16] Notably, the triaryl-substituted chiral carbon centers are difficult to make by current asymmetric methods owing to the lack of sufficient steric difference between the aryl rings.[17]

We obtained the X-ray crystal structure of the dimeric Pd complex **2b**, which was synthesized by reacting diphenyl(2-pyridyl)methane (**2**) with $Pd(OAc)_2$ in CH_2Cl_2 at 60°C (Scheme 1). The structure of **2b** suggested a working model for the chiral recognition of prochiral C–H bonds as shown in

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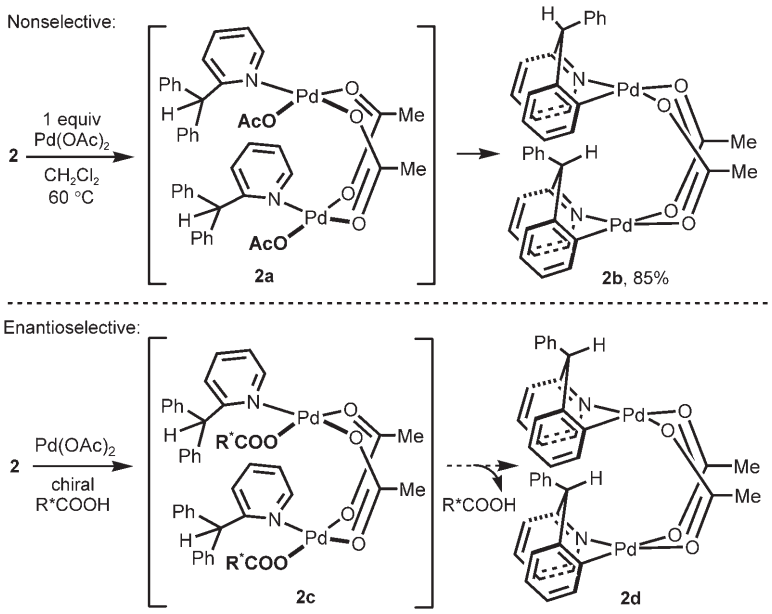
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Proposed working model for the enantioselective C–H activation of a prochiral C(sp^2)–H bond in compound **2**.

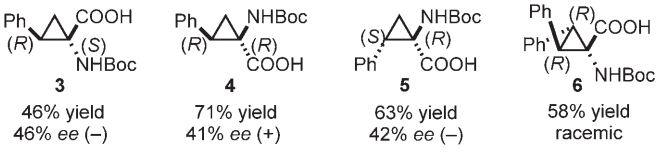
Scheme 1. We propose that enantioselective C–H activation can be achieved by replacing the nonbridging acetates in the precursor **2a** with chiral carboxylates while maintaining the bridging acetates to preserve the restricted steric environment necessary for the chiral recognition. The key question, therefore, became whether the conformation of the coordinated chiral carboxylic acids in **2c** would be sufficiently restricted to lead to good enantioselection. We had some reason for optimism, since we had previously shown that the involvement of a trinuclear μ-bridging Pd^{II} complex with similar topology was crucial for the diastereoselective iodination and acetoxylation of prochiral C–H bonds using a classical chiral-auxiliary approach.[18] In that example, however, the chiral influence came from a chiral center in the functional group of the substrates.

We therefore evaluated a number of commercially available chiral carboxylates for the enantioselective C–H activation of substrate **1**. Although we were pleased to obtain selectivities of around 20% *ee* with 20 mol% of the chiral carboxylate ligands (see the Supporting Information), improving upon these results by optimizing reaction conditions or by using other chiral carboxylates or phosphoric acids proved challenging.[19]

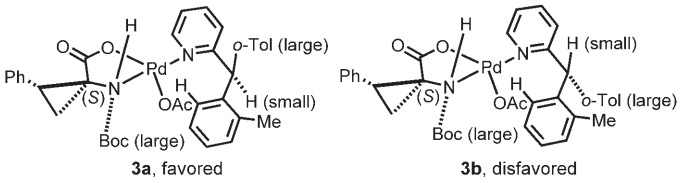
In retrospect, the poor enantioselectivity observed with chiral carboxylic acids is not entirely surprising since the R^* group is relatively free to rotate. This could lead to different chiral environments with opposite senses of chiral induction, thus resulting in the erosion of enantioselectivity. We therefore sought to restrict the possible conformations in the backbone of the chiral carboxylic acids. It has been established that adjacent substituents on cyclopropane exert significant steric repulsion owing to their eclipsed conformation, which results in effective conformational restriction.[20] Indeed, butylation of **1** using cyclopropane amino acid **3** under the previously described conditions afforded **1a** in 46% yield and 46% *ee* (Scheme 2). To gain insight into the origin of the improved enantioselectivity, we evaluated ligands **3**–**6**. While the opposite enantioselectivities obtained with the enantiomeric pair **3** and **5** are expected, the switch of the sense of chiral induction between **3** and **4** suggests that the chirality of the α-carbon center plays a dominant role. Most strikingly, the use of ligand **6** afforded racemic alkylation products which were not expected from the mechanistic model shown in Scheme 1.

Based on these experimental data and the previously established coordination mode between acetyl-protected amino acids and Pd^{II} metallacycles,[21] we hypothesize that both the NH moiety and the carboxylate coordinate with the Pd^{II} center in a bidentate manner in the precursors (Scheme 3). Surprisingly, the NH moiety is not deprotonated, as indicated by ^{1}H NMR data in the literature.[21] The pyridine from the substrate is likely to coordinate in a *trans* position relative to the carbamate nitrogen based on a known analogous structure.[21] In the cyclopalladation step, the driving force to minimize the steric repulsion between the substitutents on the newly generated chiral center and the Boc group on the nitrogen center will favor **3a** over **3b** when chiral ligand **3** is used. The resulting cyclopalladated complexes then react with $BuB(OH)_2$ to give the enantiomerically pure products and Pd^0 which will be reoxidized to regenerate Pd^{II} species for the next catalytic cycle. It is worth noting that the sense of the chiral induction could be reversed if the conformation of the cyclic transition state is drastically different from **3a** and **3b**. The determination of the absolute configuration of the products and the cyclopalladated intermediates will offer further insights into the origin of the stereoselectivity.

The lack of enantioselectivity with ligand **6** is consistent with the revised mechanistic model, as the steric difference of



Scheme 2. Cyclopropane amino acid ligands used for the enantioselective butylation of compound **1**.



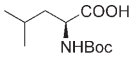
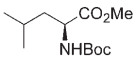
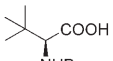
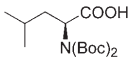
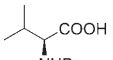
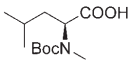
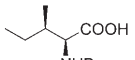
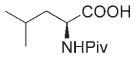
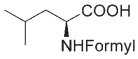
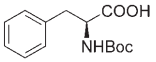
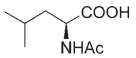
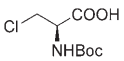
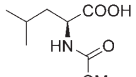
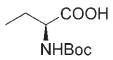
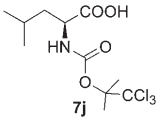
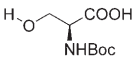
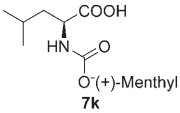
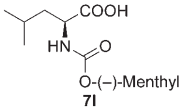
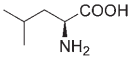
Scheme 3. Key intermediates in the mechanism for the enantioselective C–H activation. Boc = *tert*-butyloxycarbonyl, *o*-Tol = *ortho*-tolyl.

the α-carbon in **6a** is minimized. Therefore, we reasoned that the use of Boc-protected amino acids could lead to improved enantioselectivity owing to the larger steric difference between the α-hydrogen and the side chain. Gratifyingly, the asymmetric C–H activation/C–C coupling reaction of **1** in the presence Boc-L-leucine **7a** gave the alkylation product **1a** in 90% *ee* and 63% yield (entry 1, Table 1).[22] The Boc-protected amino acids **8**–**15** afforded selectivities of 52–88% *ee* (entries 2–9, Table 1).

The replacement of the Boc by a methyl group or removal of the Boc group led to a full recovery of the starting material, suggesting that an electron-withdrawing group attached to the N atom is necessary to maintain the electrophilicity of the Pd^{II} catalyst for C–H activation (entries 10 and 11, Table 1). Systematic structural modifications of **7a** indicated the following important information consistent with our model. First, esterification of **7a** leads to a complete loss of *ee* (entry 12, Table 1). Second, the use of diprotected amino acids **7d** and **7e**, or **7f** containing a poor coordinating NHPiv group, afforded the alkylated product in less than 10% *ee* (entries 13–15, Table 1). Third, the reduction in the sizes of the protecting group from Boc to methoxycarbonyl, acetyl, and formyl groups resulted in steady decrease of selectivity (entries 16–18, Table 1).

Based on this information, we replaced the Boc group in ligand **7a** with a bulkier menthoxycarbonyl group and discovered that ligands **7k** and **7l** gave greatly improved yields and also good *ee* values (entries 20 and 21, Table 1). The lack of influence of the chirality of the menthyl group on

Table 1: Influence of the ligand on enantioselectivity of the butylation of **1**.[a]

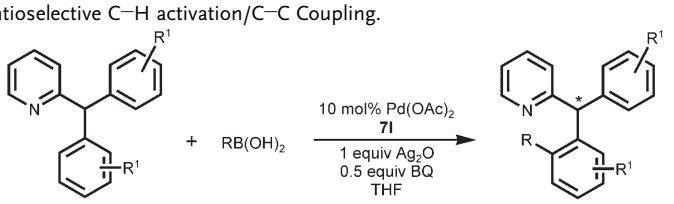
Entry	Ligand	Yield [%][b]	*ee* [%][c]	Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	 **7a**	63	90	12	 **7c**	86	0
2	 **8**	60	52	13	 **7d**	74	7
3	 **9**	69	70	14	 **7e**	63	6[d]
4	 **10**	85	72	15	 **7f**	58	7
5	 **11**	60	80	16	 **7g**	53	6
6	 **12**	66	81	17	 **7h**	74	80
7	 **13**	83	83	18	 **7i**	88	79
8	 **14**	47	85	19	 **7j**	89	85
9	 **15**	65	88	20	 **7k**	87	85
10	 **16**	n.r.[e]	–	21	 **7l**	91	87
11	 **7b**	n.r.[e]	–				

[a] All reactions were performed with **1** (0.2 mmol) and $BuB(OH)_2$ (0.6 mmol) in the presence of $Pd(OAc)_2$ (10 mol%), chiral ligand (20 mol%), benzoquinone (0.5 equiv), and Ag_2O (1.0 equiv) in 2 mL of anhydrous THF at 60°C for 20 h. Piv = pivaloyl. [b] Yields were based on isolated products. [c] Enantiomeric excesses (*ee* values) were determined by HPLC on a chiral stationary phase. [d] The opposite enantiomer was obtained. [e] No reaction.

the enantioselectivity is also consistent with the proposed mechanistic model (Scheme 3).

With ligand **7l** in hand, we further optimized reaction conditions and obtained the product in 95% *ee* at 50°C (entry 2, Table 2). Importantly, the ligand load could be reduced to 10 mol% without affecting the enantioselectivity

Table 2: Enantioselective C–H activation/C–C Coupling.

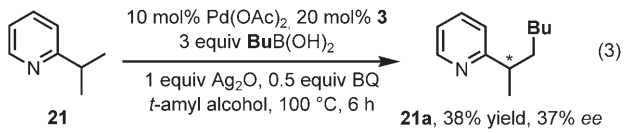


Entry	Substr.	R^1	R	*T* [°C]	**7l** [mol%]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**1**	*o*-Me	*n*Bu	60	20	20	91	87
2	**1**	*o*-Me	*n*Bu	50	20	20	50	95
3	**1**	*o*-Me	*n*Bu	60	10	20	96	88
4	**2**	H	*n*Bu	80	20	20	47	79
5	**2**	H	*n*Bu	80	10	20	56	74
6	**1**	*o*-Me	Et	60	10	20	81	84
7	**1**	*o*-Me	Cy[c]	60	10	20	61	89
8[d]	**17**	*m*-Me	*n*Bu	60	10	40	58	84
9[d]	**18**	*m*-OMe	*n*Bu	80	10	20	55	54
10[d]	**19**	*m*-OAc	*n*Bu	80	10	20	43	72
11	**20**	*p*-Me	*n*Bu	80	10	20	61	78

[a] Yield of isolated product. [b] *ee* values were determined by HPLC on a chiral stationary phase. [c] Cy = cyclopropyl. [d] Alkylation occured only at the less hindered position.

(entries 3, 5–11, Table 2,). The high yield also suggests that this ligand does not affect the reaction adversely. We are pleased to find that this enantioselective alkylation reaction can also be used with other boronic acids (entries 6 and 7, Table 2,). Not surprisingly, substrates **17**–**20** lacking *ortho* substituents react with lower enantioselectivity; this can be explained by the reduction in steric bulk (entries 8–11, Table 2,).

To test whether this protocol can be extended to enantioselective alkylation of $C(sp^3)$–H bonds, substrate **21** was subjected to the standard conditions. Poor enantioselectivity (10–15% *ee*) was obtained with ligands **7k**, **7l**, and **8** (see the Supporting Information for details). A significant improvement was made by using ligand **3** to achieve 37% *ee* [Eq. (3)]. The sensitive response of enantioselectivity to the



(3)

ligand structure suggests that there is vast potential for further tuning and the design of better ligands to achieve enantioselective C–H activation reactions with more general substrate scope. We are currently modifying this cyclopropane ligand to this end.

In summary, monoprotected α-amino acids are effective chiral ligands for Pd^{II}-catalyzed enantioselective C–H activation reactions. The coordination of a chiral nitrogen atom at the metal center is believed to be crucial for the enantiocontrol, although detailed understanding must await full characterization of the intermediates and also kinetic studies. This newly established approach for chiral recognition in the C–H activation step and the accumulated knowledge of using chiral amino acids in asymmetric catalysis[23] are likely to open new avenues for the development of enantioselective C–H activation reactions with broad substrate scope.

Experimental Section

General procedure for the alkylation reaction: In a 20 mL Teflon cap-sealed tube, the substrate (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), boronic acid (0.6 mmol, 3 equiv), Ag_2O (46.3 mg, 0.2 mmol, 1 equiv), benzoquinone (10.8 mg, 0.1 mmol, 0.5 equiv), and **7l** (6.3 mg, 0.02 mmol, 10 mol%) were dissolved in 2 mL of anhydrous THF under atmospheric air. The tube was sealed with a Teflon-lined cap, and the reaction mixture was stirred at the desired temperature. The reaction mixture was filtered through a pad of Celite, and the Celite was washed with 20 mL of CH_2Cl_2. The filtrate was concentrated under vacuum. The residue was then purified by column chromatography on silica gel with hexanes/ethyl acetate and enantiomeric excess (*ee*) was determined by HPLC on a chiral stationary phase (see the Supporting Information).

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Keywords: amino acids · boronic acids · C–C coupling · C–H activation · enantioselectivity

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