C–H Activation

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Enantioselective C–H Olefination of α-Hydroxy and α-Amino Phenylacetic Acids by Kinetic Resolution

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Abstract: *Significant progress has been made in the past decade regarding the development of enantioselective C–H activation reactions by desymmetrization. However, the requirement for the presence of two chemically identical prochiral C–H bonds represents an inherent limitation in scope. Reported is the first example of kinetic resolution by a palladium(II)-catalyzed enantioselective C–H activation and C–C bond formation, thus significantly expanding the scope of enantioselective C–H activation reactions.*

Development of enantioselective C–H activation reactions is a significant and challenging task in catalysis and organic synthesis as they offer new disconnections for asymmetric synthesis.[1] Among various approaches,[2–7] the palladium-catalyzed desymmetrization of prochiral C–H bonds has emerged as a promising avenue that can lead to a wide range of enantioselective carbon–carbon[8,9] and carbon–heteroatom bond-forming reactions.[10] However, desymmetrization is only suitable for substrates containing two prochiral C–H bonds, thus limiting the structural diversity that can be accessed by this approach. For example, the previously reported (Figure 1 a) enantioselective palladium(II)-catalyzed C–H olefination of diphenylacetic acids using mono-N-protected amino acid (MPAA) ligands cannot be applied to the preparation of important chiral derivatives of mandelic acids and phenylglycines.[8b]

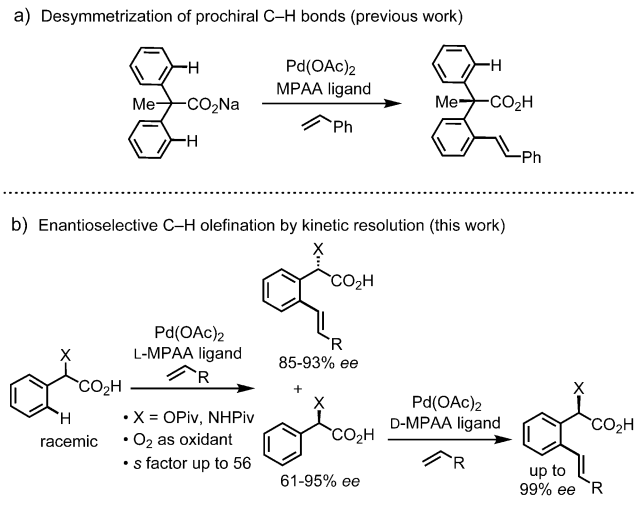

Figure 1. Enantioselective C–H activation reactions.

Enantiopure α-hydroxy and α-amino phenylacetic acids, also known as mandelic acids and phenylglycines, respectively, are important structural motifs found in many pharmaceuticals and biologically active compounds such as the antibiotics cefamandole, cephalexin, and vancomycin.[11] Enantioenriched mandelic acid and phenylglycine derivatives can also be utilized as catalysts, as well as chiral building blocks in organic synthesis.[12] As a consequence, asymmetric syntheses of these two families of compounds have received much attention.[13,14] An early example of asymmetric hydroxylation of benzylic C–H bonds of chiral epoxides[15] and the recent development of enantioselective C–H iodination using Pd^{II}/MPAA catalysts demonstrate the feasibility of achieving kinetic resolution[16] through C–H hydroxylation and iodination. Herein, we report a palladium(II)-catalyzed enantioselective C–H olefination of α-hydroxy and α-amino phenylacetic acids through kinetic resolution to afford enantiomerically enriched olefinated mandelic acids and phenylglycines (Figure 1 b). The remaining starting materials are further enantioselectively olefinated using chiral MPAA ligands, with the opposite configuration, to give the enantiomer in high enantiomeric purity. Notably, these chiral molecules are not accessible through desymmetrization of prochiral C–H bonds or other asymmetric methods.[13,14] To the best of our knowledge, this reaction is the first example of kinetic resolution by C–H activation and C–C bond formation.

We commenced our studies by exploring the enantioselective C–H olefination/kinetic resolution of the racemic pivaloyl (Piv) protected 3-chloromandelic acid *rac*-**1a** with methyl acrylate as the coupling partner (Table 1; see the Supporting Information for screening of the O-protecting group). It was found that in the presence of Boc-L-Ala-OH (**L1**) as the ligand, the enantioselective C–H olefination of *rac*-**1a** under aerobic conditions afforded the desired product $\mathbf{2a_1}$ with 89% *ee* at 18% conversion, thus corresponding to a selectivity factor (*s*)[17] of 21 (entry 1). Encouraged by this promising result, we screened a variety of Boc-protected amino acid ligands with different side chains (**L1**–**L6**). The *s* factors were gradually improved with the increase of the steric bulk on the side chains (entries 1–6). In particular, both Boc-L-Tle-OH (**L5**) and Boc-L-Thr(*t*-Bu)-OH (**L6**) gave superior *s* factors of 38 (entries 5 and 6). As the hydroxy group on threonine (H-L-Thr-OH) could provide a valuable handle for structural modifications, this amino acid was selected as the ligand backbone for further tuning. Firstly, we investigated the effect of different N-protecting groups. While Fmoc-L-Thr(*t*-Bu)-OH (**L8**) provided a similar *s* factor to that

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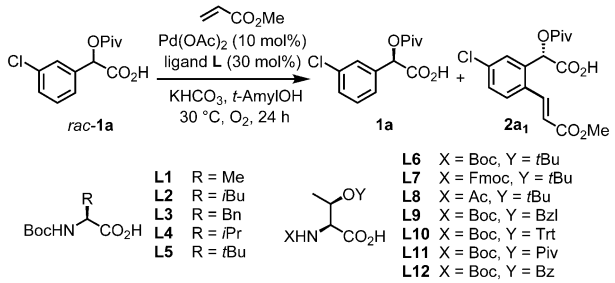
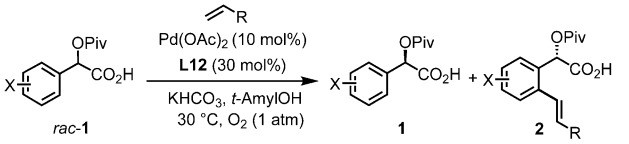
Table 1: Screening of MPAA ligands.[a]



Entry	L	Ligand	Conv. [%][b]	*ee* [%][c] 1a	*ee* [%][c] 2a$_1$	*s*
1	**L1**	Boc-L-Ala-OH	18	19	89	21
2	**L2**	Boc-L-Leu-OH	35	47	87	22
3	**L3**	Boc-L-Phe-OH	42	63	86	25
4	**L4**	Boc-L-Val-OH	46	74	86	29
5	**L5**	Boc-L-Tle-OH	47	79	88	38
6	**L6**	Boc-L-Thr(*t*-Bu)-OH	45	74	89	38
7	**L7**	Fmoc-L-Thr(*t*-Bu)-OH	24	29	93	37
8	**L8**	Ac-L-Thr(*t*-Bu)-OH	52	88	80	26
9	**L9**	Boc-L-Thr(Bn)-OH	34	47	90	30
10	**L10**	Boc-L-Thr(Trt)-OH	49	81	84	29
11	**L11**	Boc-L-Thr(Piv)-OH	48	82	90	48
12	**L12**	Boc-L-Thr(Bz)-OH	49	87	90	54
13[d]	**L12**	Boc-L-Thr(Bz)-OH	46	77	89	40
14[e]	**L12**	Boc-L-Thr(Bz)-OH	45	75	91	48
15[f]	**L12**	Boc-L-Thr(Bz)-OH	40	62	93	51

[a] Reaction conditions: *rac*-**1a** (0.2 mmol), methyl acrylate (0.6 equiv), $Pd(OAc)_2$ (10 mol%), ligand (30 mol%), $KHCO_3$ (2.0 equiv), *t*-AmylOH (1.0 mL), O_2 (1 atm), 30°C, 24 h. [b] Calculated conversion, $c = ee_{SM}/(ee_{SM} + ee_{PR})$. [c] Determined by chiral-phase HPLC analysis. [d] At 40°C, 12 h. [e] Using $Pd(OAc)_2$ (5 mol%), **L12** (15 mol%), 48 h. [f] Using 0.4 equiv of methyl acrylate. Boc = *tert*-butoxy carbonyl, Fmoc = 9-fluorenylmethoxycarbonyl.

Table 2: Enantioselective C–H olefination/ kinetic resolution of mandelic acids.[a]

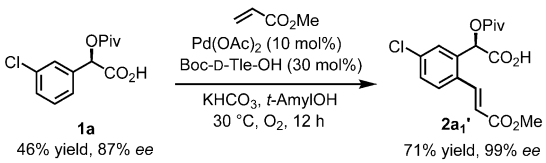


Entry	*rac*-**1**	X	R	*t* [h]	Conv. [%][b] (Yield [%])[c]	*ee* [%][d] **1**	*ee* [%][d] **2**	*s*
1	*rac*-**1a**	3-Cl	CO_2Me	24	49 (45)	87	90	54
2	*rac*-**1a**	3-Cl	CO_2Et	24	48 (46)	83	90	48
3	*rac*-**1a**	3-Cl	CO_2Bn	24	45 (41)[e]	73	91	46
4	*rac*-**1a**	3-Cl	$CONMe_2$	24	46 (43)[e]	77	92	56
5	***rac*-1a**	3-Cl	$PO(OEt)_2$	24	47 (42)	80	91	52
6	*rac*-**1a**	3-Cl	COMe	36	42 (39)	67	92	48
7	*rac*-**1a**	3-Cl	Ph	24	48 (46)	82	90	48
8	*rac*-**1b**	3-CF_3	CO_2Me	48	38 (35)	58	93	50
9	*rac*-**1c**	3-Me	CO_2Me	24	44 (43)	70	89	36
10	*rac*-**1d**	3-Ph	CO_2Me	24	42 (41)	64	90	37
11	*rac*-**1e**	3-OPiv	CO_2Me	24	41 (40)	65	92	47
12	*rac*-**1f**	4-CF_3	CO_2Me	60	43 (38)[f]	65	92	26
13	*rac*-**1g**	4-F	CO_2Me	60	42 (37)[f]	61	90	22
14	*rac*-**1h**	4-Cl	CO_2Me	60	41 (35)[f]	59	90	22
15	*rac*-**1i**	4-OMe	CO_2Me	48	45 (41)[f]	67	86	20
16	*rac*-**1j**	3,4-Cl_2	CO_2Me	48	49 (40)	86	89	50
17	*rac*-**1k**	3-OMe-4-OPiv	CO_2Me	48	47 (43)	75	85	28
18	*rac*-**1l**	H	CO_2Me	24	43 (39)[f]	64	91	23
19	*rac*-**1a**	3-Cl	CO_2Me	27	52 (48)	95	86	49

[a] Reaction conditions: *rac*-**1** (0.2 mmol), olefin (0.6 equiv), $Pd(OAc)_2$ (10 mol%), **L12** (30 mol%), $KHCO_3$ (2.0 equiv), *t*-AmylOH (1.0 mL), O_2 (1 atm), 30°C, 24–60 h. [b] Calculated conversion, $c = ee_{SM}/(ee_{SM} + ee_{PR})$. [c] Yield of the isolated olefinated product. [d] Determined by chiral-phase HPLC analysis. [e] To simplify separation, the crude mixture containing the olefinated product was methylated using $TMSCH_2N_2$. [f] Determined by ^1H NMR analysis of the crude reaction mixture.

of **L6,** albeit with much lower reactivity (entry 7, $s = 37$), Ac-L-Thr(*t*-Bu)-OH (**L7**) resulted in a marked decrease in the *s* factor (entry 8, $s = 26$). Based on these results, a number of different hydroxy protecting groups on Boc-L-Thr-OH were investigated. Both the protecting groups benzyl (Bn) and trityl (Trt) led to a slight decrease in selectivity (entries 9 and 10). Gratifyingly, acyl protecting groups such as Piv and benzoyl (Bz) significantly improved the selectivity with Boc-L-Thr(Bz)-OH (**L12**) and gave the best *s* factor of 54 (entries 11 and 12). When the temperature was raised to 40°C, the reaction was greatly accelerated, albeit with a slightly decreased *s* factor (entry 13). With an extended reaction time, the loading of $Pd(OAc)_2$ could be reduced to 5 mol% without significantly affecting the selectivity (entry 14). Besides, a decrease in the amount of olefin to 0.4 equivalents improved the *ee* value of the olefinated product to 93% with a decreased conversion of 40% (entry 15).

With the optimized reaction conditions in hand, we investigated the substrate scope of the protocol. The enantioselective C–H olefination of *rac*-**1a** with different olefin coupling partners were carried out (Table 2). The reaction worked well with a wide range of electron-deficient olefins (entries 1–7). Acrylates were excellent coupling partners, thus affording the corresponding olefinated products **2a$_1$**–**a$_3$** with *s* factors ranging from 46 to 54 (entries 1–3). Vinyl amides and vinyl phosphates were well tolerated (entries 4 and 5). Alkyl vinyl ketones were also compatible with this kinetic resolution reaction, although a slightly longer reaction time was required (entry 6). Coupling with the less reactive styrene also proceeded smoothly to give the olefinated product **2a$_7$** in 90% *ee* (entry 7). Importantly, a wide range of substituted mandelic acid substrates were successfully olefinated with synthetically useful *s* factors. The reaction of substrates bearing both electron-withdrawing (CF_3, F, Cl) and electron-donating (Me, Ph, OMe, and OPiv) groups gave the corresponding products with *s* factors ranging from 20 to 50 (entries 8–17). All the *meta*-substituted substrates were regioselectively olefinated at *para* to the 3-substituent (entries 8–11). The chlorine atom in products **2a$_1$**–**a$_7$**, **2h**, and **2j** can potentially serve as a useful handle for subsequent synthetic elaboration. 3,4-Disubstituted substrates were also compatible with this protocol (entries 16 and 17). The unsubstituted substrate also provided the desired product in 39% yield with 91% *ee* (entry 18). Although the *s* factors obtained with *para*-substituted and unsubstituted substrates were somewhat lower, the enantiomeric purities of the desired products were still satisfactory (entries 12–15 and



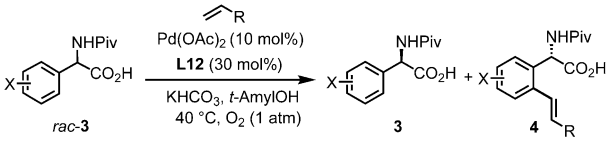
Scheme 1. Enantioselective C–H olefination of the recovered starting material.

18). Notably, high enantiomeric purity of starting material could be obtained when the conversion was slightly above 50%. For example, (*R*)-3-chloromandelic acid (**1a**) was recovered in 95% *ee* at 52% conversion (entry 19). Moreover, subjecting the recovered starting material (*R*)-**1a**, which was isolated in 46% yield and 87% *ee* (entry 1), to enantioselective C–H olefination conditions using a MPAA ligand with the opposite configuration afforded the chiral product (*R*)-$\mathbf{2a_1}$ in 99% *ee* (Scheme 1), thus demonstrating the feasibility of obtaining both enantiomers of the olefinated mandelic acids through this approach. More importantly, the removal of the Piv protecting group can be accomplished in high yields under alkaline conditions without any loss of stereochemical purity (see the Supporting Information for the cleavage of Piv group), thus rendering this reaction a practical method for the synthesis of chiral mandelic acid derivatives.

We next turned our attention to the kinetic resolution of racemic phenylglycine derivatives. Considering the potential bis(dentate) coordination of the substrate with the palladium(II) center could interfere with the ligand, our initial effort focused on the identification of an appropriate N-protecting group. Indeed, when using Boc and Ac as the protecting group, the kinetic resolution reaction provided the olefinated products in good yields but with very poor enantioselectivities. We were pleased to find that the racemic Piv-protected 3-chlorophenylglycine *rac*-**3a** was successfully olefinated at elevated temperature (40 °C) to give **4a** with high selectivity (Table 3, entry 1). Both electron-withdrawing (Cl, F) and electron-donating (OMe) substituents on the aryl ring were well tolerated, thus furnishing the olefinated products with good *s* factors (entries 2–4). Notably, the kinetic resolution of the racemic phenylglycine *rac*-**3e** gave exclusively the mono-olefinated product $\mathbf{4e_1}$ with synthetically useful selectivity (entry 5). The reaction also worked well with the less reactive styrene to give the olefinated product $\mathbf{4e_2}$ with a high *s* factor (entry 6).

The absolute configuration of **2f** was determined by X-ray crystallography analysis to be *S*[18] and prompted us to propose a stereomodel to rationalize the origin of the selectivity. According to previous extensive structural and computational studies,[8a,19] we proposed two possible transition states, $\mathbf{TS_S}$ and $\mathbf{TS_R}$ (Figure 2). In both $\mathbf{TS_S}$ and $\mathbf{TS_R}$ palladium is coordinated with the MPAA ligand and the substrate in a square-planar coordination. The side-chain of amino acid points upward, which pushes the Boc groups below the palladium coordination plane to avoid steric repulsion. In the C–H activation step, the transition state $\mathbf{TS_R}$ is expected to be disfavored relative to $\mathbf{TS_S}$ because of the steric repulsion between Boc and OPiv in $\mathbf{TS_R}$, and is consistent with the faster formation of the product with the

Table 3: Enantioselective C–H olefination/ kinetic resolution of phenylglycines.[a]



Entry	*rac*-**3**	X	R	*T* [h]	Conv. [%][b] (Yield [%])[c]	*ee* [%][d] **3**	**4**	*s*
1	*rac*-**3a**	3-Cl	CO_2Me	48	47 (41)	79	91	51
2	*rac*-**3b**	4-Cl	CO_2Me	72	48 (43)	83	90	49
3	*rac*-**3c**	4-F	CO_2Me	72	45 (38)	72	88	34
4	*rac*-**3d**	4-OMe	CO_2Me	48	45 (40)	70	87	30
5	*rac*-**3e**	H	CO_2Me	10	47 (45)	79	89	41
6	*rac*-**3a**	H	Ph	10	48 (44)	81	88	39

[a] Reaction conditions: *rac*-**3** (0.2 mmol), olefin (0.6 equiv), $Pd(OAc)_2$ (10 mol%), **L12** (30 mol%), $KHCO_3$ (2.0 equiv), *t*-AmylOH (1.0 mL), O_2 (1 atm), 40 °C, 10–72 h. [b] Calculated conversion, $c = ee_{SM}/(ee_{SM} + ee_{PR})$. [c] Yield of the isolated olefinated product. [d] Determined by chiral-phase HPLC analysis.

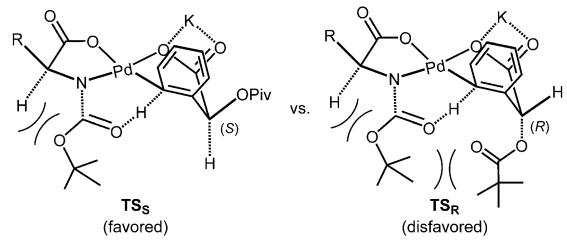


Figure 2. The proposed transition-state model.

S configuration. This arrangement could also explain why a better selectivity factor was achieved when using the bulky pivaloyl group as an O-protecting group for mandelic acids.

In conclusion, palladium(II)-catalyzed enantioselective C–H olefination of α-hydroxy and α-amino phenylacetic acids by kinetic resolution has been achieved using a mono-N-protected amino acid (MPAA) ligand, thus filling an important gap in the field of enantioselective C–H activation reactions. To the best of our knowledge, this development represents the first example of kinetic resolution by C–H activation/C–C bond formation,[20] thus providing a new approach for making C–C bonds asymmetrically.

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Keywords: amino acids · C–H activation · enantioselectivity · kinetic resolution · palladium

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