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Palladium-Catalyzed [3+2] Cycloaddition via Two-Fold 1,3-C(sp³)-H Activation

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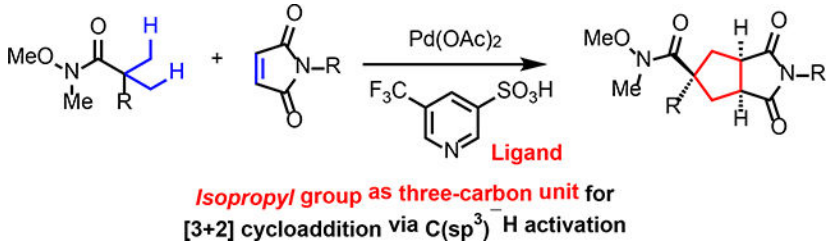
Abstract

Cycloaddition reactions provide an expeditious route to construct ring systems in a highly convergent and stereoselective manner. For a typical cycloaddition reaction to occur, however, the installation of multiple reactive functional groups (π-bonds, leaving group, etc.) are required within the substrates, compromising the overall efficiency or scope of the cycloaddition reaction. Here, we report a palladium-catalyzed [3+2] reaction that utilizes two-fold C(sp^3)–H activation to generate the three-carbon unit for formal cycloaddition. The initial β-C(sp^3)–H activation of aliphatic amide, followed by maleimide insertion, triggers a relayed, second C(sp^3)–H activation to complete a formal [3+2] cycloaddition. The key to success was the use of weakly coordinating amide as the directing group, as previous studies have shown that Heck or alkylation pathways are preferred when stronger-coordinating directing groups are used with maleimide coupling partners. To promote the amide-directed C(sp^3)–H activation step, the use of pyridine-3-sulfonic acid ligands is crucial. This method is compatible with a wide range of amide substrates, including lactams, which lead to spiro-bicyclic products. The [3+2] product is also shown to undergo a reductive desymmetrization process to access chiral cyclopentane bearing multiple stereocenters with excellent enantioselectivity.

Graphical Abstract



Synthetic methods that allow the facile construction of cyclic structures are of great importance in organic synthesis. In particular, cycloaddition reactions can serve as powerful

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Supporting Information

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Experimental procedures and spectral data for all new compounds (PDF)

tools to expedite the synthesis of ring-containing molecules,[1] as witnessed by the numerous applications of the [4+2] Diels-Alder reaction in the total synthesis of natural products.[2] While the direct analogue of the Diels-Alder reaction for the synthesis of cyclopentanes would be a [3+2] reaction, the generation of an appropriate three-carbon unit and the subsequent control of its reactivity for cycloaddition is significantly challenging (Scheme 1A).[3] Indeed, methods that directly generate free trimethylenemethane (TMM) intermediates as three-carbon units for [3+2] reactions require specifically designed substrates with limited applicability.[4] Strategies to generate TMM-equivalents with transition metal catalysts have also been developed.[5] For instance, Trost and coworkers pioneered the use of Pd-TMM complexes as intermediates for various [3+2] reactions,[6] which has been further expanded to asymmetric variants for the preparation of chiral cyclopentanes.[7] However, the generation of these TMM-equivalents still requires the precursors to be highly activated, either by ring-strain or multiple pre-functionalization. While other elegant cycloaddition approaches for cyclopentane synthesis have also been developed,[8] multiple π-bonds or leaving groups are required to be installed within the substrates. Given the abundance of five-membered rings in complex natural products and bioactive molecules,[9] a complementary [3+2] method that can directly use simple, abundant substrates, such as carboxylic acids or amides, would be highly attractive.

Pd-catalyzed diverse C–H functionalization can provide transformative disconnections *via* directly converting inert C–H bonds into versatile C–Pd bonds.[10] In this regard, we questioned whether C(sp^3)–H activation can be applied to allow a simple, unfunctionalized three-carbon propane skeleton to be used for [3+2] cycloaddition, where the C(sp^3)–H bonds of a *gem*-dimethyl moiety are formally stitched into a double bond (Scheme 1B). Inspired by the norbornene-relayed 1,2-C(sp^2)–H activation,[11] we envisioned that an analogous olefin-relayed two-fold 1,3-C(sp^3)–H activation process could be harnessed to achieve the desired [3+2] cycloaddition. However, it is noteworthy that while the norbornene-relay involves a favorable five-membered cyclopalladation with C(sp^2)–H bonds, the proposed 1,3-C(sp^3)–H activation process would require a six-membered cyclopalladation with inert C(sp^3)–H bonds, which is highly challenging.

To test this hypothesis, we turned our attention to using maleimide as the relaying olefin instead of norbornene for two reasons. First, the resulting product from maleimide would have significant synthetic utility compared to the resulting product from norbornene. Second, maleimides are reactive cyclic olefins that have been used as coupling partners for Pd-catalyzed C(sp^3)–H functionalization. However, the key maleimide-inserted intermediate (**I**) can preferably undergo undesired formal β-hydride elimination (Heck product **II**) or protonation (alkylation product **III**) pathways instead of the relayed C(sp^3)–H activation pathway (Scheme 1C). For instance, the reaction between pivalic acid and maleimide has been demonstrated to exclusively form the Heck product *via* formal β-hydride elimination.[12] Also, it has been shown that the formation of net alkylation product *via* a [C(sp^3)–Pd] protonation pathway is favored with strongly coordinating bidentate directing groups.[13] These divergent reactivities imply that the fate of the maleimide-inserted species (**I**) can be altered by employing either a new directing group or a ligand. We speculated that using a weakly coordinating directing group might promote the relayed C(sp^3)–H activation due to

the more facile release of the Pd center from the directing group, which would be essential for the Pd center to re-orient for the second C(sp^3)–H activation. In this sense, our recent development of the pyridinesulfonic acid ligand allowed us to exploit the weakly coordinating carbonyl group of amides as the directing group.[14] To our delight, using amide substrates led to the exclusive formation of [3+2] products (**V**), presumably *via* the intermediacy of the dialkylpalladacycle intermediate (**IV**). Here, we report the development of a catalytic [3+2] cycloaddition between amide substrates and maleimides that operates *via* Pd-catalyzed two-fold C(sp^3)–H activation.

We first evaluated the ligand effect for the reaction between pivalic amide **1** and *N*-(4-nitrophenyl)maleimide (Table 1). Without using any ligand, 10% yield of the cyclopentane product was observed along with trace amounts of the Heck product. While using *N*-acetylglycine (**L1**) or pyridone (**L2**) ligands led to improved results compared to the ligand-free conditions, the use of pyridine-3-sulfonic acid (**L3**) as the ligand gave the desired product in significantly increased yield. In accordance with the previous result in the Pd-catalyzed C(sp^3)–H olefination reaction,[14b] more electron-deficient **L4** proved to be the optimal ligand for the [3+2] reaction. As shown in Table 1, the Heck product was only observed as the minor product in all cases, indicating that the [3+2] pathway is predominant regardless of the nature of the ligand. It is also noteworthy that when pivalic acid was subjected to the identical [3+2] reaction conditions with **L4**, only the Heck product was observed, implying that the use of the weakly coordinating amide directing group is crucial to achieve the [3+2] pathway (See Supplementary information). The high level of diastereoselectivity observed in the [3+2] product prompted us to further analyze its stereochemistry. First, regarding the fused bicyclic core, the [3+2] product displayed a *cis*-ring junction, strongly supporting our mechanistic hypothesis that the second C(sp^3)–H activation occurs in a relayed manner. Second, the configuration of the major diastereomer exhibited a *cis*-relationship between the imide group and the directing group, whereas the minor diastereomer exhibited a *trans*-relationship, indicating that the second C(sp^3)–H activation step is selective between the two remaining methyl groups. Overall, the diastereoselectivity profile of the [3+2] reaction highly resembles that of a typical pericyclic cycloaddition reaction, in a sense that the relationships between multiple stereocenters are controlled.

With the optimal ligand in hand, the substrate scope of the [3+2] reaction was examined (Table 2). First, various substituents on the amide carboxyl group were tested (Table 2A). Simple alkyl (**2**–**3**), aryl (**4**), and heteroatom-containing functional groups (**5**–**8**) were all tolerated to give the desired cyclopentane products. Substrates containing saturated heterocycles (**9**–**12**) were also suitable substrates for the [3+2] reaction. To our disappointment, substrates bearing α-hydrogens were incompatible. Given that C(sp^3)–H olefination process works with these substrates under nearly identical reaction conditions,[14b] it is supposed that the second C–H activation step (six-membered palladacycle formation without any quaternary carbon center in between) becomes problematic. Next, the scope of the amino group of the substrate was investigated (Table 2B). Substrates bearing dialkylamino groups with varying sterics (**13**–**15**) and cyclic amino groups (**16**–**21**) successfully provided the corresponding products. Amino acid-derived substrates (**22**–**23**)

also gave the products in good yields, as well as Weinreb amide (**24**) and *N*-Aryl (**25**) substrates. While secondary amides (**26**–**28**) also underwent the desired reaction, electron-deficient maleimide was required to achieve high yields. In general, simple *N*-phenylmaleimide is less reactive compared to electron-deficient maleimides which are more activated Michael acceptors, especially with secondary amides which afford lower yields compared to tertiary amides due to the Thorpe-Ingold effect. The effect of the maleimide *N*-substitution was also systematically studied (Table 2C). Among the *N*-arylmaleimides, both electron-rich (**29**–**30**) and electron-deficient (**31**–**35**) maleimides gave high yields and diastereoselectivities. *Ortho*- and *meta*-substituted *N*-arylmaleimides (**36**–**37**) were suitable coupling partners as well. Electron-rich *N*-heteroarylmaleimides (**38**–**39**) also provided the products in high yields, although slightly lower diastereoselectivities were observed. *N*-alkylmaleimides proved to be highly reactive coupling partners, regardless of the nature of the *N*-substituents (**40**–**44**). When other related electron-deficient olefins, such as maleic anhydride, were tested, [3+2] products were not observed (See Supplementary Information). Finally, lactams were tested as substrates for the [3+2] reaction (Table 2D). Such a process would provide a unique disconnection towards the elusive spiro-bicyclic products bearing cyclopentane motifs. To our delight, the six-membered lactam (**45**) provided the desired bicyclic product in 47% yield. Seven-membered or larger lactams (**46**–**48**) served as highly reactive substrates to give the bicyclic products in good yields. Functionalized seven-membered lactams (**49**–**51**), as well as 1,4-diazepanone derived substrate (**52**) were also suitable for the [3+2] reaction. Overall, the major diastereomers in all cases showed *cis*-relationship between the imide group and the amide directing group. Since the diastereomeric ratios cannot be rationalized by sterics alone, we hypothesize that attractive interactions through dispersion between the two polar groups could be one important factor.

To further demonstrate the synthetic utility, the [3+2] reaction was carried out on gram-scale without any loss of efficiency (Scheme 3A). As a cheaper alternative for the silver oxidant, copper salt could also serve as the terminal oxidant for the gram-scale [3+2] reaction, albeit in diminished yields (See Supplementary Information for oxidant screening). We also attempted to access chiral cyclopentanes *via* reductive desymmetrization of the [3+2] products using chiral oxazaborolidine catalysis (Scheme 3B).[15] Following the procedures developed by Jones and coworkers,[16] the [3+2] product **20** underwent desymmetrization with (1*S*,2*R*)-*cis*-1-aminoindan-2-ol derived catalyst to yield the hydroxylactam **53**. Then, **53** was directly converted into lactam **54** for analytical purpose. To our delight, 98% ee was observed with **54**,[17] although only 45% yield was obtained based on recovered starting material. The low yield is due to the over-reduction that leads to the formation of pyrrolidine byproduct. Nevertheless, the combined sequence of diastereoselective [3+2] cycloaddition and enantioselective reduction allows one to rapidly synthesize novel chiral cyclopentane compounds with multiple stereocenters.

An alternative mechanistic pathway where the Heck product is formed first, followed by a second C(sp^3)–H activation/intramolecular migratory insertion is also worth consideration. Although such a process would lead to a *trans*-fused bicyclic core due to the *syn*-addition of [C–Pd], rapid epimerization to the thermodynamic *cis*-fused product may allow us to obtain the observed [3+2] product. To check the viability of this mechanistic pathway, Heck

product **55** was prepared and subjected to the reaction conditions (Scheme 4). Regardless of the presence of maleimide, the formation of [3+2] product **20** was not observed, implying that the Heck product is not an intermediate for the [3+2] pathway.

In summary, a catalytic [3+2] reaction between *gem*-dimethyl-containing amide substrates and maleimides *via* two-fold C(sp^3)–H activation is developed. The employment of the weak-coordinating amide directing groups was essential to unlock the [3+2] pathway, as other directing groups have been previously reported to give either Heck or alkylation products. To enable such an amide-directed C(sp^3)–H activation, the use of an electron-deficient pyridine-3-sulfonic acid was crucial. A diverse array of cyclopentane products were obtained in a diastereoselective manner, including spiro-bicyclic compounds derived from lactam substrates. Using chiral oxazaborolidine catalysis, we demonstrated that the [3+2] product can be desymmetrized to give a chiral cyclopentane in excellent enantioselectivity. Given that both C(sp^3)–C(sp^3) bonds are directly forged from C(sp^3)–H bonds without the need for pre-functionalization, we anticipate that this method would complement the conventional strategies for cyclopentane synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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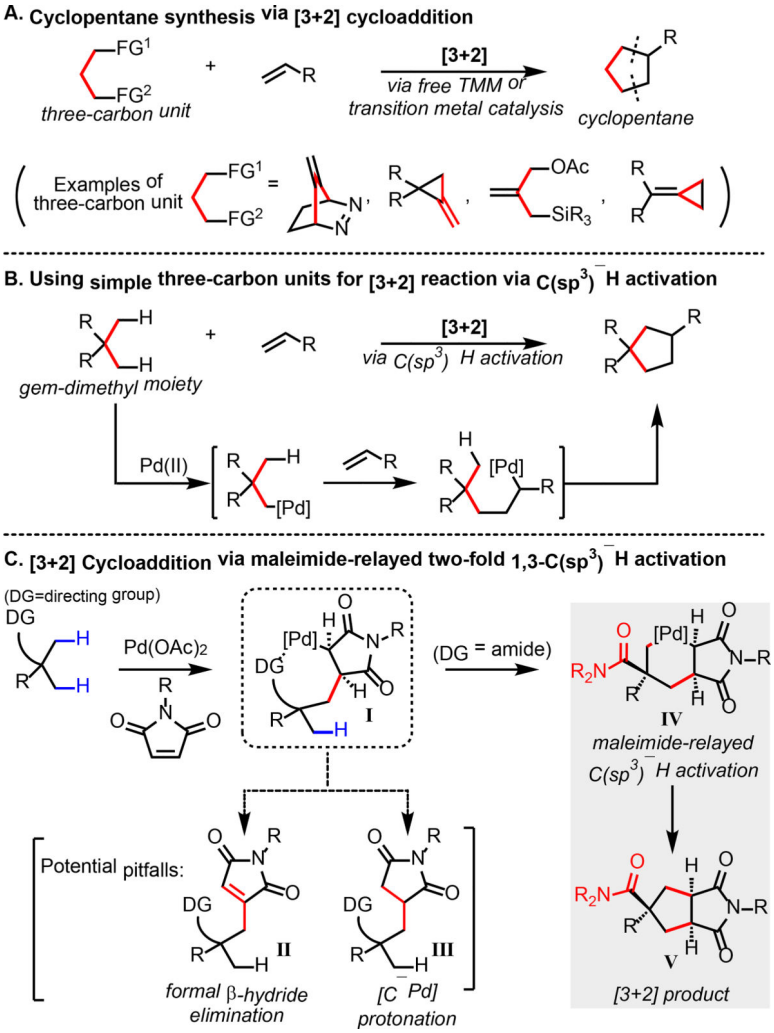
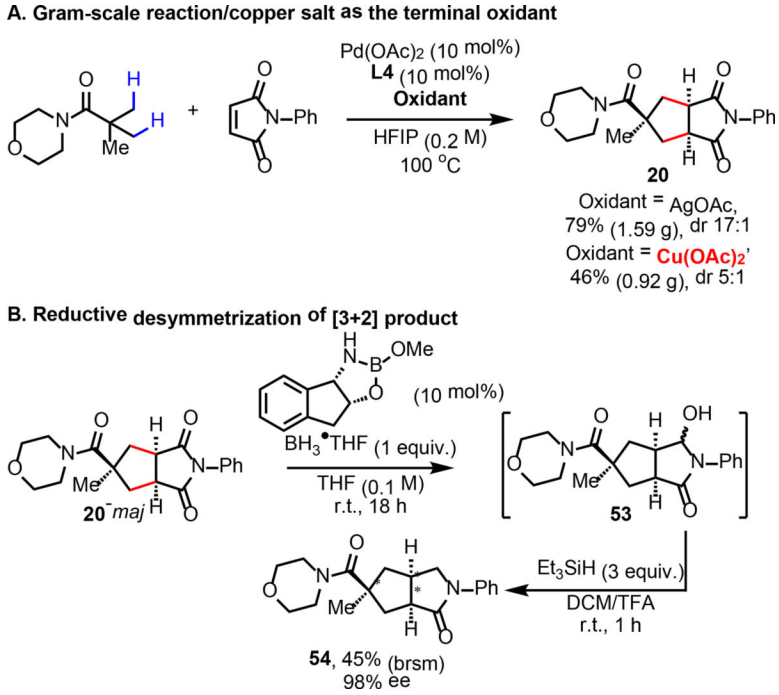
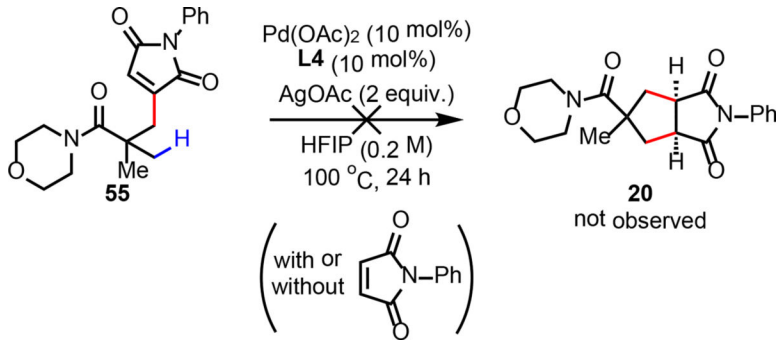


Scheme 1.
[3+2] Cycloaddition reaction



Scheme 3.

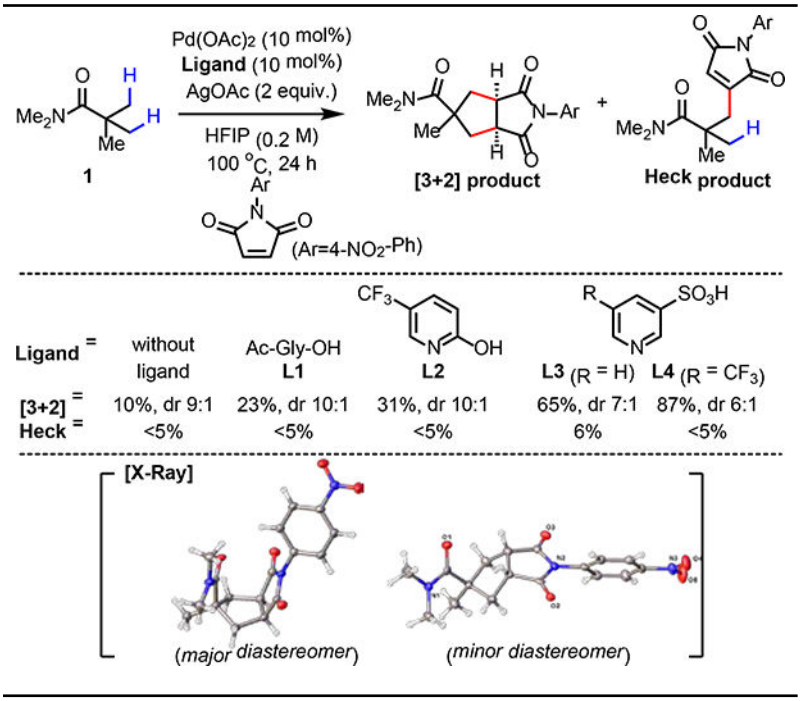
Gram-scale reaction/Reductive desymmetrization of cyclopentane product



Scheme 4.
Attempted reaction with Heck product 55

Table 1.

Evaluation of ligands[a,b]



[a]Conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), Ligand (10 mol%), *N*-(4-nitrophenyl)maleimide (0.15 mmol), AgOAc (0.2 mmol), HFIP (0.5 mL), 100 °C, 24 h.

[b]The yield and diastereomeric ratio were determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

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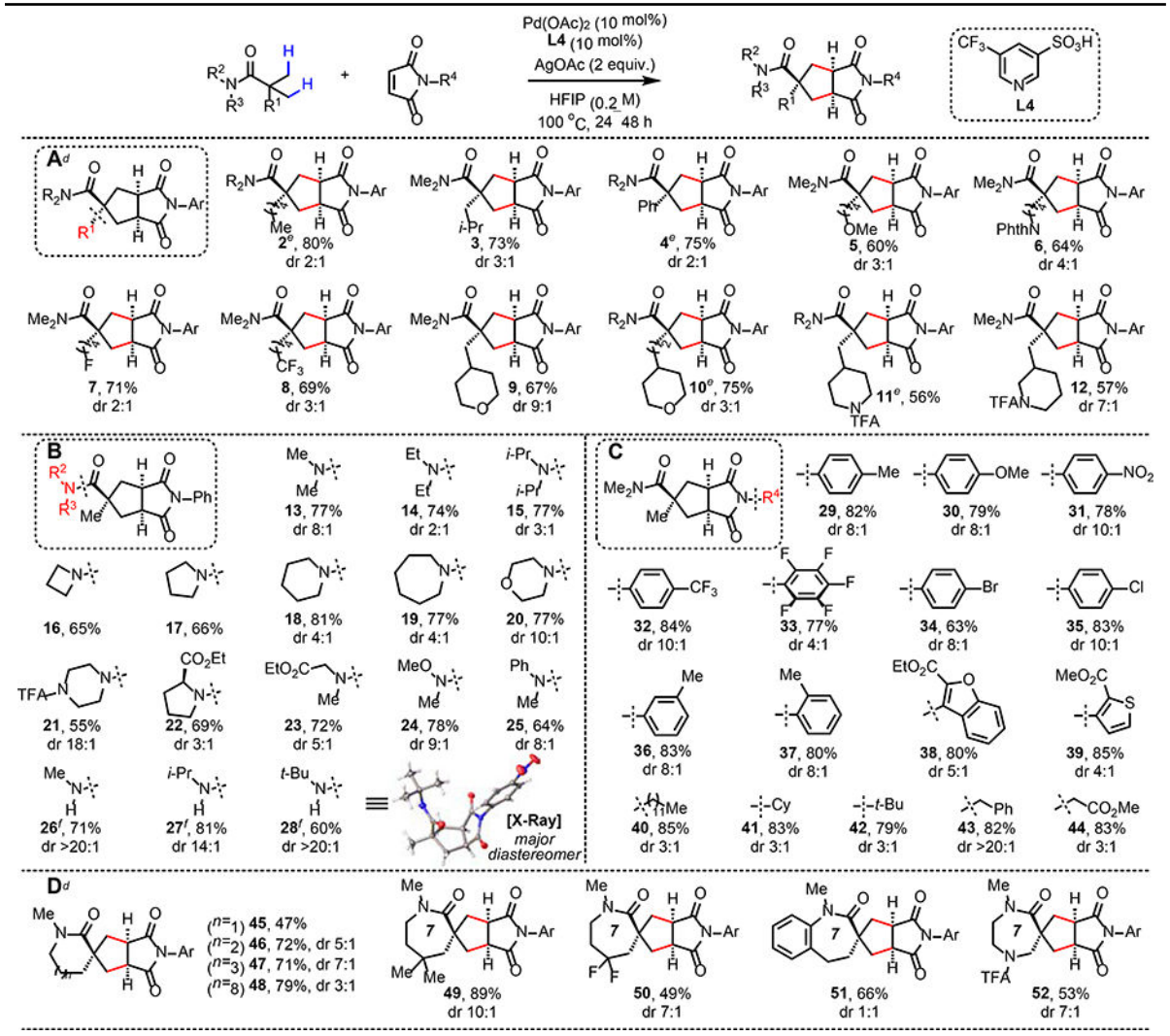
Table 2.

Substrate scope of [3+2] cycloaddition reaction[a,b,c]



[a] Conditions: amide substrate (0.1–0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L4** (10 mol%), maleimide (1.5 equiv.), AgOAc (2 equiv.), HFIP (0.2 M), 100 °C, 24–48 h. See Supplementary Information for details.

[b] Isolated yield/diastereomeric ratio.

[c] The isolated diastereomeric ratio does not necessarily reflect the diastereoselectivity of the reaction.

[d] *N*-(4-(trifluoromethyl)phenyl)maleimide was used.

[e] R_2NH = piperidine.

[f] *N*-(4-nitrophenyl)maleimide was used.